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TAXONOMIC COMPOSITION OF ZOOPHILIC FLIES IN SAMARKAND

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Zoophilic flies (Diptera) are a group of insects closely associated with livestock farms and veterinary-sanitary conditions. Many species act as mechanical vectors of various pathogens, negatively affecting livestock productivity. Information on the fauna, ecology, and taxonomy of zoophilic flies in Uzbekistan and neighboring regions has been reported by several researchers [1, 7, 8]. However, data on the current taxonomic composition of zoophilic flies in the Samarkand region remain insufficient. Therefore, the aim of this study was to determine the species composition and taxonomic structure of zoophilic flies in the Samarkand region.

The study was conducted in different natural and anthropogenic biotopes of the Samarkand region. Specimens were collected using entomological nets, sticky traps, and bait traps. In the laboratory, samples were examined under a binocular microscope and identified using standard taxonomic keys.

For the identification of Diptera families, the key by E.P. Narchuk was used, while species identification and classification were based on works by A. Stackelberg, G. Bey-Bienko, N. Violovich, and the monograph Flies and Disease [2, 4, 6].

The study was carried out during 2016–2025 in various ecological zones and livestock farms of the Samarkand region. As a result, 90 species belonging to 42 genera and 14 families were identified. The distribution of species among families showed significant differences.

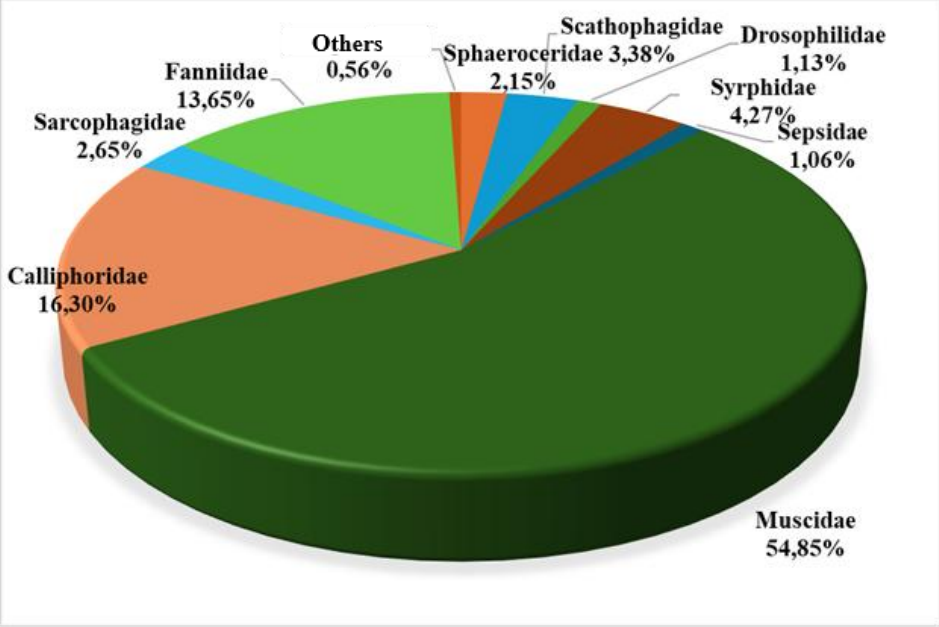

Figure 1. Proportion of zoophilic fly families in Samarkand region (%)

The family Muscidae was the dominant group, comprising 54.85% of the total fauna. This dominance is explained by its high ecological adaptability, strong reproductive capacity, and close association with livestock environments. Similar findings have been reported by other researchers [5, 9, 10].

The second most abundant family was Calliphoridae (16.30%), followed by Fanniidae (13.65%). Other families included Syrphidae (4.27%), Scathophagidae (3.38%), Sarcophagidae (2.65%), Sphaeroceridae (2.15%), Drosophilidae (1.13%), and Sepsidae (1.06%). The remaining families collectively accounted for 0.56% of the total fauna.

These results confirm that Muscidae represents the dominant ecological group in the zoophilic fly fauna of the Samarkand region, due to its strong ecological plasticity and adaptation to livestock environments.

Conclusion. The study confirmed that the family Muscidae is the leading taxonomic group in the zoophilic fly fauna of the Samarkand region. The obtained results are important for assessing regional biodiversity and developing effective veterinary-sanitary control measures.

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Economic sciences

TEARS TO PERFORMANCE: CONCEPTUAL FRAMEWORK FOR UNDERSTANDING MOTIVATIONAL TURNING POINTS IN MANAGEMENT, MARKETING, AND HUMAN RESOURCE DEVELOPMENT

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Abstract

Emotional resistance is one of the most universal yet systematically misunderstood challenges in management, marketing, and human resource development. All managers encounter team members who refuse to engage. Every marketer faces consumers who will not convert. Every trainer works with learners who have shut down. And yet certain outstanding practitioners, exceptional teachers, leaders, and coaches consistently transform resistance into willing, high-quality engagement through a brief, specific intervention. This paper asks what that intervention is and how it works. Drawing on a widely observed case of a four-year-old child who refuses to play the piano and then, following a single teacher intervention, plays with full absorbed engagement, we develop the Trigger Model of Motivational Turning Points: an original four-phase conceptual framework describing the transition from active emotional resistance to intrinsically motivated performance. The model integrates Self-Determination Theory, psychological reactance theory, emotional regulation theory, and flow theory into a unified architecture organized around the concept of the motivational trigger, a specific stimulus that shifts the individual's internal appraisal of the situation and activates intrinsic motivation rather than enforcing compliance. Four trigger types are identified and theoretically grounded: cognitive reframe, autonomy activation, competence activation, and relatedness activation. Five empirically testable propositions derived from the model constitute the research agenda for validation. The framework contributes the first systematic theoretical model of the motivational turning point, with direct applications for leadership practice, consumer persuasion, and human resource development across management and marketing contexts.

Keywords: *emotional resistance, motivational trigger, turning point, leadership, consumer behavior, self-determination theory, reactance theory, human resource development, flow theory, conceptual framework.*

1. Introduction

Picture a four-year-old child at a piano. He does not want to be there. His face is red. His shoulders are tense. He is crying with the full-body commitment young children bring to genuine distress. Everyone in the room has accepted that he will not play. Then the teacher says something, a single, brief intervention. The tears are slow. The child turns to the keyboard. And he plays, not reluctantly, not minimally, but with the absorbed, intrinsically motivated engagement that every music teacher, every manager, every marketer, and every trainer spends their career trying to create. What happened at that moment?

This question sits at the intersection of three of the most practically important challenges in contemporary management, marketing, and human resource development. In management, it is the challenge of the resistant employee, the team member who will not engage with a task, no matter how clearly the objective is explained, how generous the incentive, or how direct the instruction. In marketing, it is the challenge of the resistant consumer, the potential customer who has heard the pitch, understood the value proposition, and still said no. In human resource development, it is the challenge of the resistant learner, the professional who sits in a training program, arms crossed, determined not to engage. These three challenges are structurally identical. They all involve an individual in a state of active motivational resistance and a practitioner trying to create willing engagement. And they all encounter the same unresolved problem in scholarly literature: the transition moment itself has never been systematically theorized.

The motivation literature is extensive. Self-Determination Theory (SDT) [2] has provided the most comprehensive account of why people engage with activities. Transformational leadership research [3] has identified the qualities that enable leaders to inspire followers. Emotional regulation theory [4] has mapped how emotional states can be altered. Consumer behavior research has documented purchase resistance extensively [5]. What is missing across all these traditions is systematic analysis and modeling of the motivational turning point, the specific, brief, critical moment when a resistant individual becomes a willing one. This gap is not merely theoretical. It has direct and costly practical consequences: managers who cannot create turning points rely on compliance through pressure; marketers who cannot create turning points lose conversions that were theoretically achievable; trainers who cannot create turning points deliver programs whose content never reaches the resistant learner.

This paper addresses this gap by developing the Trigger Model of Motivational Turning Points: a four-phase conceptual framework describing how emotional resistance transitions to intrinsically motivated performance through a specific motivational trigger. The model integrates SDT [2], Brehm's reactance theory [1], Gross's emotional regulation model [4], and Csikszentmihalyi's flow theory [6] into a unified architecture. Four trigger types are identified: cognitive reframe, autonomy activation, competence activation, and relatedness activation, each of which is theoretically grounded in SDT's three fundamental psychological needs. Five empirically testable propositions derived from the model constitute the research agenda for future validation studies across management, marketing, and human resource development contexts.

The paper makes three contributions to existing literature. First, it introduces the Trigger Model as the first systematic theoretical framework for understanding and explaining the motivational turning point. Second, it derives a four-type trigger taxonomy that is both theoretically grounded and practically actionable. Third, it establishes a cross-disciplinary bridge among motivation research, leadership theory, emotion regulation theory, and consumer behavior within a unified framework applicable across management, marketing, and educational practice.

2. Literature Review

This section reviews five bodies of theoretical and empirical scholarship that together form the foundation of the Trigger Model: psychological reactance and emotional resistance; Self-Determination Theory; emotional regulation and cognitive neuroscience; leadership and the turning point; and consumer resistance and the Yes Moment. The review identifies the specific gap the Trigger Model addresses and situates the paper's contribution within existing literature.

2.1. Psychological Reactance and Emotional Resistance

Resistance, as theorized in this paper, is defined as an active motivational state in which an individual refuses engagement with a demanded task or behavior. Brehm [1] first theorized this as psychological reactance: when individuals perceive their freedom to choose being threatened, they experience a motivational drive to restore that freedom, producing oppositional cognition, negative affect, and behavioral refusal. Brehm and Brehm [7] extended this analysis to demonstrate that reactance is most acute when the demand is perceived as controlling rather than autonomy-supportive, and that direct attempts to overcome reactance through pressure or argument typically intensify rather than reduce it.

In organizational contexts, emotional resistance is documented as a primary barrier to change management [8], training effectiveness [9], and leadership effectiveness [10]. Oreg's [8] individual differences measure of resistance to change identifies four dispositional components: routine seeking, emotional reaction, short-term focus, and cognitive rigidity, each of which intensifies under pressure. In marketing contexts, Puntoni et al. [5] demonstrate that AI-driven personalized marketing can produce resistance that conventional persuasion techniques cannot overcome, and Cialdini [19] documents the specific social conditions that reliably reduce resistance and produce compliance. What both the organizational and marketing literatures lack, however, is a theoretical account of the reversal of resistance the moment when the resistant individual becomes willing. This paper provides that account.

2.2. Self-Determination Theory and the Psychology of Intrinsic Motivation

Deci and Ryan's [2] Self-Determination Theory provides the most influential and empirically supported framework for understanding why people engage with activities. SDT identifies three fundamental psychological needs: autonomy (the need to experience one's actions as self-chosen), competence (the need to feel effective in interaction with the environment), and relatedness (the need to feel connected to others) as universal prerequisites for intrinsic motivation. When these needs are satisfied, individuals engage with activities for their inherent value. When they are frustrated, individuals either disengage or engage only under external pressure, producing the compliance-without-performance dynamic that resistant employees, resistant consumers, and resistant learners exemplify.

SDT's identification of these three needs as the universal motivational prerequisites is directly incorporated into the Trigger Model. Each of the model's four trigger types activates one or more of these needs: cognitive reframe activates competence; autonomy activation restores the sense of self-determination; competence activation affirms capability; relatedness connects the task to valued relationships. The trigger is not a manipulation technique; it is a need-satisfaction intervention that creates the intrinsic motivational conditions under which genuine engagement becomes possible [11].

2.3. Emotional Regulation and the Neuroscience of State Shifts

Gross's [4] process model of emotion regulation established that emotional states can be deliberately altered through cognitive reappraisal, changing how a situation is understood, rather than suppressing the emotional response or changing the situation itself. Cognitive reappraisal is most effective when deployed early in the emotional generation process, before the emotional response is fully consolidated and before it has recruited behavioral commitments such as the explicit refusal that characterizes active resistance [15].

The neuroscientific basis of the motivational turning point lies in the interaction between the amygdala and the prefrontal cortex. When an individual experiences emotional resistance, the amygdala's threat-detection function generates a threat response that prioritizes self-protection over task engagement, narrowing attentional scope and inhibiting approach motivation [16]. An effective trigger, particularly a cognitive reframe, activates the prefrontal cortex's regulatory capacity, reducing the amygdala's threat signal and enabling the attention broadening that Fredrickson's [24] Broaden-and-Build Theory identifies as the precondition for positive emotional engagement. This is the neurological mechanism by which the turning point occurs: not the suppression of resistance, but the transformation of the internal appraisal that generates it.

2.4. Transformational Leadership and the Turning Point

Bass and Avolio's [3] transformational leadership framework identifies four components of leadership that move followers beyond immediate self-interest: idealized influence, inspirational motivation, intellectual stimulation, and individualized consideration. Each of these components involves a specific form of reframing, presenting the task, the relationship, or the follower's identity in a way that activates higher-level motivation than the immediate context would naturally produce. The transformational leader, in the Trigger Model's terms, is the practitioner with the broadest and most flexibly deployed trigger repertoire.

Motivational interviewing [17], originally developed as a clinical technique for producing behavior change in resistant individuals with substance use disorders, provides the most developed practitioner-level framework for trigger deployment. Its four core processes, engaging, focusing, evoking, and planning, correspond closely to the four phases of the Trigger Model, and its specific techniques, reflective listening, open questions, affirmations, and summarising, map directly onto the autonomy-activation and relatedness-activation trigger types. The Trigger Model extends motivational interviewing's clinical framework to management, marketing, and educational practice, providing the theoretical grounding that motivational interviewing's pragmatic development has not always supplied [17].

2.5. Consumer Resistance and the Yes Moment

Consumer resistance to persuasion is extensively documented in marketing research. Knowles and Linn [20] distinguish approach-based and avoidance-based resistance, noting that most persuasion research focuses on overcoming avoidance-based resistance through argument and evidence, while approach-based resistance, the more common form in marketing contexts, requires activating positive approach motivation rather than refuting negative avoidance reasons. Fogg's behavior model identifies motivation, ability, and prompt as the three components of behavior change, implying that resistant consumers can be moved to action by the right prompt at the right moment, the Yes Moment theorized by the Trigger Model.

The consumer turning point, the specific moment when a consumer's internal state shifts from resistance to willingness, has not been systematically modeled in the existing consumer behavior literature. Cialdini's [19] influence principles provide a catalog of social triggers that reliably produce compliance, but they are analyzed as persuasion techniques rather than as mechanisms of motivational turning points. The Trigger Model reframes them as triggers that activate specific psychological needs, providing a theoretically grounded account of why they work and when each type is most effective. This reframing has direct practical implications: it suggests that the most effective consumer turning points activate intrinsic motivation rather than merely produce compliance, thereby generating brand advocacy and post-purchase satisfaction that compliance-based conversion does not.

2.6. The Literature Gap

The five bodies of scholarship reviewed above have each made essential contributions to understanding motivation, resistance, and engagement. What none of them has done is theorize the transition moment itself, the specific, brief, critical instant when a resistant individual becomes a willing one. Motivation research studies sustained motivation over time. Emotional regulation research studies how individuals manage emotions across extended periods. Leadership research studies how leaders maintain follower engagement across relationships and careers. Consumer behavior research studies the antecedents and consequences of resistance without modeling its reversal. The motivational turning point sits in the space between these traditions, and it is the space the Trigger Model occupies.

3. The Trigger Model of Motivational Turning Points

3.1. Overview and Four-Phase Architecture

The Trigger Model describes the transition from active emotional resistance to intrinsically motivated performance in four phases. Table 1 presents the complete model, its theoretical basis, and its applications in management, marketing, and education.

Table 1. The Trigger Model of Motivational Turning Points: phases, mechanisms, and applications

Phase	What happens	Theoretical basis	Organizational / marketing application
Phase 1Resistance	Individuals experiences active refusal, emotional distress, and motivational shutdown	Reactance theory [1]; Gross emotional regulation model [4]	Employee refuses task; consumer rejects marketing; learner disengages from training
Phase 2The Trigger	A specific stimulus shifts the individual's internal appraisal of the situation	Self-Determination Theory [2]; Cognitive reappraisal [15]	Leader reframes the task; marketer activates intrinsic motivation; coach restores sense of autonomy
Phase 3: The Turning Point	Rapid reduction in negative effect; resistance dissolves; willingness emerges	Broaden-and-Build Theory [24]; Motivational interviewing [17]	Employee commits to the task; consumer moves toward purchase; learner re-engages with the content
Phase 4Performance	Intrinsically motivated engagement produces absorbed, sustained, high-quality output	Flow theory [6]; Growth mindset [23]	Employee exceeds expectations; consumer becomes brand advocate; learner achieves mastery

Source: Authors' theoretical synthesis.

3.2. Phase 1: Resistance Understanding the State We Are Working With

In the Trigger Model, resistance is not a character flaw or a behavioral problem. It is a structured psychological state with identifiable neurological, motivational, and behavioral components. At the neurological level, resistance involves amygdala-mediated threat activation, which narrows the attentional scope and inhibits approach motivation [16]. At the motivational level, it involves the frustration of one or more of SDT's three fundamental psychological needs: the individual feels that their autonomy is being overridden, that they lack the competence to succeed, or that the task is disconnected from the relationships and identities that matter to them [2]. At the behavioral level, it manifests as explicit refusal, emotional expression, or withdrawal.

This structural analysis has an important practical implication. Because resistance is a structured state with identifiable motivational causes, it is theoretically reversible through interventions that address those causes. The practitioner who understands which needs are being frustrated can design an intervention that activates the need and its trigger, thereby dissolving resistance at its source rather than attempting to overcome it by force or incentive.

3.3. Phase 2: The Trigger What Creates the Turning Point

The trigger is the model's central and most original contribution. A trigger, as defined in the Trigger Model, is a specific stimulus, verbal, behavioral, or environmental, that shifts the resistant individual's internal appraisal of the situation in a way that activates intrinsic motivation. The trigger does not force compliance. It does not overcome resistance through pressure. It transforms the internal conditions generating resistance, so that resistance dissolves and willingness emerges.

The Trigger Model identifies four trigger types, each corresponding to the activation of one of SDT's fundamental psychological needs. Table 2 presents the complete trigger taxonomy with definitions, activated needs, and practical examples.

Table 2. The Trigger Taxonomy: four trigger types, definitions, and applications

Trigger type	Definition	SDT need activated	Example in practice
Cognitive reframe	Changing how the individual appraises the task or situation, not the task itself	Competence: task reframed as achievable	'You already know how to do this you did something harder last month'
Autonomy activation	Restoring the individual's sense of choice within the constrained situation	Autonomy: freedom of choice restored	'You don't have to do this right now. When do you think would work best for you?'
Competence activation	Affirming the individual's existing capability before introducing the challenge	Competence: confidence in ability activated	'You are one of the people I trust most with this kind of challenge'
Relatedness activation	Connecting the task to a relationship or identity that matters to the individual	Relatedness: social connection activated	'Your team needs this from you specifically. No one else can do what you do here'

Source: Authors' theoretical derivation from Self-Determination Theory [2].

The cognitive reframe trigger works at the level of situation appraisal: it changes how the individual understands the task without changing the task itself. In the piano video, the teacher's intervention was most likely a cognitive reframing, perhaps connecting the piano to something the child already loved, reframing the difficulty as a matter of familiarity rather than a threat, or reframing the performance as play rather than evaluation. The autonomy activation trigger restores the individual's sense of agency within the constrained situation: it does not change the requirement but changes the individual's experience of their relationship to it. Competency activation triggers affirmation of existing capability before introducing the challenge; it directly addresses the threat-to-competence that is generating resistance. The relatedness activation trigger connects the task to a valued relationship, making it meaningful by grounding it in the social context that matters to the individual.

3.4. Phase 3: The Turning Point What Happens in the Moment

The turning point is the observable manifestation of the internal state shift produced by the trigger. It is characterized by a rapid reduction in negative affect, a shift in body posture and facial expression, and the initiation of task-directed behavior. In the piano video, the turning point is clearly visible: the tears slow, the shoulders drop, and the child turns to the keyboard. This transition is not the result of compliance achieved through pressure; it is the result of willingness achieved through transformation.

Fredrickson's [24] Broaden-and-Build Theory provides the psychological mechanism. When the amygdala's threat signal is reduced by the trigger, the individual's attentional scope broadens from the narrow, threat-focused state of resistance to the open, opportunity-oriented state that characterizes positive effect and approach motivation. This broadened state activates the cognitive and motivational resources that enable genuine task engagement. The turning point is, at its neurological core, the moment when the individual's brain shifts from defensive to approach mode, a shift that no amount of external pressure can produce directly, but that an effective trigger can create by transforming the internal appraisal generating the threat response.

3.5. Phase 4: Performance Why the Quality Surprises

One of the most theoretically significant features of the piano video and of effective motivational turning points more generally is that the quality of performance following the turning point consistently exceeds what would be produced by mere compliance. The piano child does not play reluctantly or minimally. He plays with absorbed engagement and evident intrinsic motivation. The same pattern is observed in management contexts when resistant employees are effectively triggered: the performance that follows the turning point characteristically exceeds the manager's expectations and the employee's own prior performance.

Csikszentmihalyi's [6] flow theory explains this phenomenon. Flow, the state of complete absorption in a task that produces optimal performance, requires intrinsic motivation: the individual must be engaged by the activity's inherent value rather than by external reward or pressure. An effective trigger, by activating intrinsic motivation rather than producing compliance, creates the necessary condition for flow. The surprising quality of post-trigger performance is not an anomaly; it is precisely what intrinsic motivation looks like in action. This has a critical practical implication: the difference between triggered performance and pressure-induced compliance is not merely a matter of the individual's comfort. It is a performance difference that is observable, measurable, and theoretically predictable.

4. Research Propositions

The Trigger Model generates five empirically testable propositions that constitute the research agenda for the model's validation. Each proposition addresses a specific theoretical claim made by the model and specifies a proposed empirical test. Table 3 presents the complete set of propositions.

Table 3. Research propositions derived from the Trigger Model

P	Proposition	Proposed empirical test
P1	Individuals who receive a cognitive reframe trigger during active emotional resistance will transition to task engagement significantly faster than those who receive directive instruction or no intervention.	Experimental design: three conditions (reframe vs. directive vs. control); N ≥ 150; measure time-to-engagement and performance quality output. Georgian professional sample.
P2	Autonomy-activating triggers will produce more sustained post-trigger engagement than compliance-producing pressure interventions, as measured by performance quality and intrinsic motivation ratings at 30-day follow-up.	Survey experiment with longitudinal follow-up; SDT Basic Psychological Needs Scale; compare intrinsic motivation activation vs. compliance across Georgian management and marketing contexts.
P3	Leaders with higher emotional intelligence will more accurately identify the specific trigger type required for each resistant individual, resulting in significantly higher turning-point success rates than leaders with lower emotional intelligence.	Multi-source assessment: Mayer-Salovey-Caruso EI Test; observation of real coaching conversations; turning point success rated by supervisor and peer independently.
P4	Consumer turning points in marketing contexts are more likely to be driven by autonomy-supportive communication than by persuasive pressure, and to yield higher post-purchase satisfaction and brand loyalty at 60 days.	Between-subjects consumer experiment: autonomy-supportive vs. persuasive message conditions; N ≥ 200; measure conversion rate, post-purchase satisfaction, and 60-day brand loyalty.
P5	Trigger effectiveness varies significantly across cultural contexts: cognitive reframe triggers are more effective in collectivist cultures, while autonomy-activation triggers are more effective in individualist cultures.	Cross-cultural comparative study: minimum three countries (Georgia, China, Germany); N ≥ 100 per country; same experimental design; Hofstede cultural dimension scales as moderators.

Source: Authors' theoretical derivation.

Propositions P1 and P2 address the model's core empirical predictions about trigger effectiveness and the sustainability of trigger-induced engagement. P1 tests whether triggers produce faster turning points than directive instruction, the most practically consequential comparison for management practice. P2 tests the SDT-derived prediction that activating intrinsic motivation yields more durable engagement than compliance, addressing the common practitioner concern that triggered engagement may not be sustained. P3 tests the emotional intelligence moderation hypothesis, providing a basis for predicting which leaders are most likely to deploy triggers effectively and which need the most development. P4 extends the model to consumer marketing contexts, providing a direct test of the Yes Moment framework and its commercial implications. P5 addresses the cross-cultural moderation that the geographic diversity of the model's proposed applications requires a particularly important proposition given that the video motivating the model's development involves a Chinese child and teacher, while the framework's primary application context is Georgian management practice.

5. Discussion

5.1. Theoretical Implications

The Trigger Model's most significant theoretical contribution is the identification of the motivational turning point as a distinct and theoretically important phenomenon that existing frameworks of motivation, leadership, and behavior have not modeled. The model's four-phase architecture — Resistance, Trigger, Turning Point, Performance provides the first systematic account of the transition from active resistance to intrinsically motivated engagement, filling a gap that cuts across multiple scholarly traditions simultaneously.

The model advances SDT [2] by specifying how the theory's three fundamental needs can be activated in real time to dissolve resistance, rather than treating need satisfaction as a background condition for sustained motivation. It advances Gross's [4] emotional regulation framework by identifying how cognitive reappraisal can be externally facilitated through specific practitioner interventions, rather than treating reappraisal as a purely internal regulatory strategy. It advances transformational leadership theory [3] by specifying the mechanism that needs to be activated by targeted triggers, through which transformational leaders produce the follower engagement that the framework's four components describe at a more abstract level. And it advances consumer behavior research [5] by providing a theoretical account of the Yes Moment, the consumer turning point that existing persuasion research has not supplied.

The Trigger Model also has implications beyond its three primary application domains. The fundamental insight that resistance is a structured motivational state that can be systematically reversed through need-activating interventions is applicable wherever human practitioners encounter motivated refusal: clinical psychology, education, negotiation, conflict resolution, and public health behavior change. The Concentration Principle that emerges from the model, that the most effective interventions concentrate on activating the specific need being frustrated rather than overcoming the behavioral manifestation of its frustration, is a general principle of motivational practice with broad applicability.

5.2. Practical Implications for Management

For managers and leaders, the Trigger Model has three immediate practical implications. First, it reframes resistance from a character problem to a motivational state problem: instead of asking 'why is this person difficult?', the effective manager asks, 'which need is being frustrated and how can I activate it?'. This reframing is practically consequential because it shifts the manager's intervention from pressure and argument, which reactance theory [1] shows typically intensify resistance to need-activation, which SDT [2] and the Trigger Model show can dissolve it.

Second, the Trigger Taxonomy provides managers with a specific, learnable repertoire of intervention types rather than the vague exhortation to 'be a better motivator'. A manager who understands that a resistant employee is experiencing a competence threat can specifically deploy a competence-activation trigger. A manager who understands that resistance reflects an autonomy threat can specifically deploy an autonomy-activation trigger. This specificity transforms trigger deployment from an instinctive gift possessed by exceptional leaders into a teachable skill available to any manager willing to learn it.

Third, the performance prediction that trigger-induced engagement characteristically exceeds compliance-induced performance provides managers with a business case for investing in trigger repertoire development that the existing leadership literature has not clearly articulated. The manager who creates motivational turning points is not merely a more pleasant workplace presence; they are generating measurably superior performance outcomes.

5.3. Practical Implications for Marketing

For marketing practitioners, the Trigger Model's most significant implication is the reframing of the conversion challenge from persuasion to need activation. The conventional persuasion framework asks: 'How do we overcome the consumer's resistance to our product?' The Trigger Model asks: 'Which psychological need can we activate to make engagement with our product intrinsically motivated rather than externally pressured?' This distinction is practically consequential because triggered engagement, the Yes Moment, produces not only conversion but also post-purchase satisfaction, brand loyalty, and advocacy that compliance-based conversion does not.

The trigger taxonomy provides marketing practitioners with a specific framework for designing conversion-oriented communications that address identified psychological needs. An autonomy-activation trigger in marketing might involve giving the consumer genuine choice within the purchase decision rather than creating artificial urgency. A competence-activation trigger might involve affirming the consumer's expertise and judgment before presenting product information. A related activation trigger might involve connecting the product to the consumer's existing value relationships rather than attempting to create a new brand relationship from a cold start. These applications are testable through Proposition P4 and provide a concrete research agenda for the emerging literature on intrinsic motivation in consumer behavior.

5.4. Practical Implications for Human Resource Development

For HRM practitioners and training designers, the Trigger Model provides both a diagnostic framework for understanding learner resistance and an intervention framework for addressing it. The model's identification of three types of need frustration that generate resistance competence threats, autonomy threats, and relatedness threats maps directly onto three common causes of training disengagement: the learner who feels the training is too difficult (competence threat), the learner who feels the training is being imposed without their genuine participation (autonomy threat), and the learner who sees no connection between the training content and their valued work relationships or identity (relatedness threat). Each cause calls for a different trigger type, and the model specifies what that trigger should look like in practice.

5.5. Limitations

This paper presents a conceptual framework and does not include primary empirical evidence. The five research propositions in Table 3 constitute the systematic agenda for addressing this limitation through future validation studies. The conceptual analysis draws on the piano video as a motivating case, but the paper does not claim that the teacher's specific intervention has been identified or that the model has been validated against that specific case. The trigger taxonomy is theoretically derived from SDT and remains to be validated empirically in management, marketing, and educational contexts across different cultures. The cross-cultural proposition (P5) is particularly important given that the piano video involves a Chinese child and teacher, while the model's primary application context is Georgian and broadly Western management practice. Cultural differences in power distance, individualism-collectivism, and attitudes toward emotional expression may substantially moderate the effectiveness of triggers in ways that the current conceptual framework cannot fully specify.

6. Conclusion

This paper asked a deceptively simple question: What happened in the moment when the crying child at the piano became the willing pianist? The answer this paper proposes is that the teacher deployed a motivational trigger a specific, brief intervention that activated one of the child's frustrated psychological needs, shifted his internal appraisal of the situation, and created the conditions for intrinsic motivation to emerge. The result was not compliance. It was genuine, absorbed, high-quality engagement. It was a motivational turning point.

The Trigger Model of Motivational Turning Points constitutes the first systematic theoretical framework for understanding and explaining this phenomenon across management, marketing, and human resource development contexts. Its four-phase architecture, Resistance, Trigger, Turning Point, Performance, provides the conceptual vocabulary for analyzing turning points wherever they occur. It triggers a cognitive reframe in taxonomy, autonomy activation, competence activation, and relatedness activation, which provide the practical repertoire for creating them intentionally. And its five research propositions provide the empirical agenda for validating its claims across the diverse contexts in which resistant individuals and skilled practitioners interact.

The significance of this framework extends beyond its three primary application domains. Every field that involves changing human behavior, medicine, public health, education, conflict resolution, negotiation, and governance, confronts the same fundamental challenge: the resistant individual who will not change. The Trigger Model offers any of these fields a theoretically grounded account of how change can be created without coercion: not by overcoming resistance but by dissolving its motivational source. The piano teacher understood this intuitively. The Trigger Model proposes to understand it scientifically and to make that understanding teachable, testable, and transferable to the management, marketing, and human resource development practitioners who need it most.

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Medical sciences

THE ROLE OF PATENT FORAMEN OVALE IN THE ETIOLOGY OF CRYPTOGENIC STROKE IN YOUNG ADULTS: A THEORETICAL REVIEW

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Abstract

Objective: To systematically analyze and evaluate the contemporary clinical data regarding the role of patent foramen ovale (PFO) in the pathogenesis of cryptogenic stroke and the clinical efficacy of its therapeutic management in young and middle-aged patients (18–60 years).

Methods: A comprehensive theoretical and clinical analysis was performed on large-scale randomized controlled trials and extensive meta-analyses sourced from the PubMed database and international collaborative research consortiums (such as the SCOPE study).

Results: Clinical data indicate that PFO is detected in approximately 50% of patients under the age of 60 who present with a cryptogenic stroke or embolic stroke of undetermined source (ESUS). Pooled data analysis confirmed that transcatheter device closure significantly reduces the annual incidence of recurrent stroke from 1.09% to 0.47% compared to medical therapy alone (adjusted Hazard Ratio [HR] = 0.41). However, the therapeutic benefit is highly heterogeneous and strongly correlates with the Risk of Paradoxical Embolism (RoPE) score and the PASCAL classification system (r = 0.95).

Conclusion: Percutaneous device closure represents the most effective secondary prevention strategy in carefully selected young patients with highly pathogenic PFO characteristics.

Keywords: *cryptogenic stroke, patent foramen ovale (PFO), paradoxical embolism, RoPE score, PASCAL classification.*

Introduction:

Ischemic stroke in young and middle-aged adults (aged 18–60 years) remains one of the most challenging and critical areas in contemporary neurocardiology and angioneurology. Because traditional cardiovascular risk factors typical of older patients (such as advanced atherosclerosis, carotid stenosis, and atrial fibrillation) are relatively rare in younger populations, standard diagnostic algorithms frequently fail to identify a definitive etiology. Cerebral ischemic events that remain unexplained after an exhaustive diagnostic workup are classified as cryptogenic strokes or embolic strokes of undetermined source (ESUS).

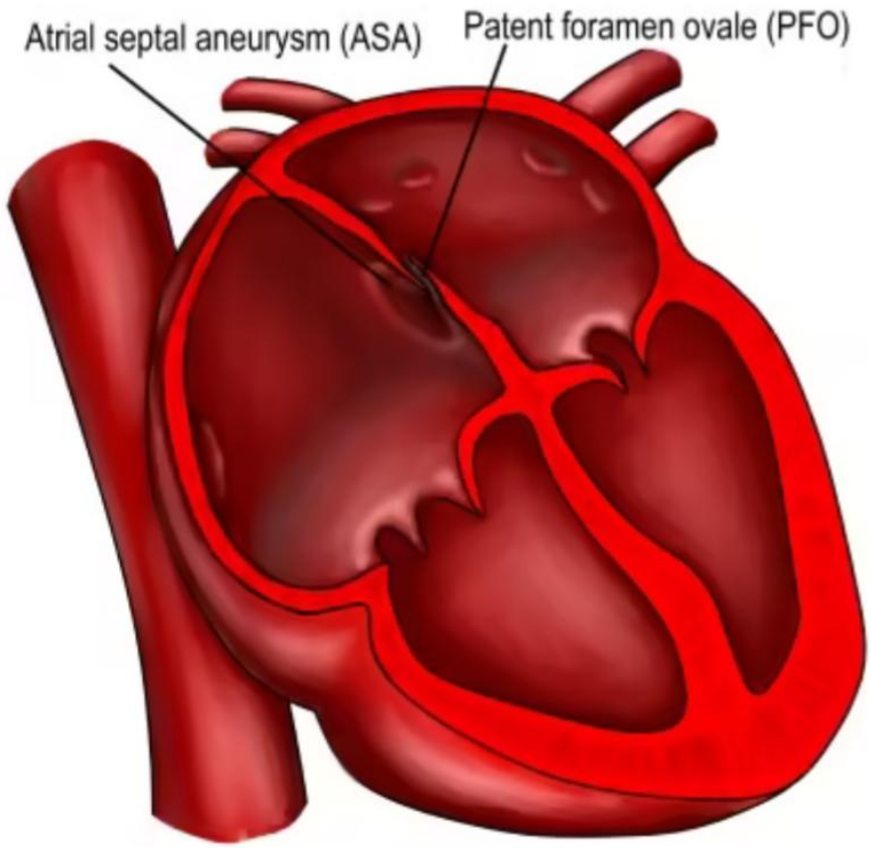
Current clinical evidence establishes that approximately 10% of all ischemic strokes in adults aged 18 to 60 years are directly associated with a patent foramen ovale (PFO). Consequently, the objective of this theoretical review is to conceptually synthesize the data from major international clinical trials and pooled meta-analyses to comprehensively elucidate the pathophysiological role of PFO, its differential diagnosis, and the comparative efficacy of current therapeutic modalities.

2. Theoretical Analysis and Authorial Subheadings

2.1. Pathophysiological Substrate and the Mechanism of Paradoxical Embolism

A patent foramen ovale (PFO) is an anatomical interatrial communication between the right and left atria that persists when the fetal secundum and primum atrial septa fail to fuse after birth. While a PFO is a common anatomical variant present in approximately 25% of the general adult population, its prevalence doubles to nearly 50% among patients under 60 years of age diagnosed with a cryptogenic stroke.

The development of a stroke in the presence of a PFO is primarily driven by the mechanism of paradoxical embolism. Thrombi or microemboli originating within the venous system (e.g., deep veins of the lower extremities or pelvic plexuses) would normally be filtered by the pulmonary circulation. However, during activities that transiently elevate right atrial pressure (such as coughing, straining, or heavy physical exertion), a transient right-to-left shunt occurs. This allows the venous thrombus to cross directly through the PFO into the left atrium, bypassing the pulmonary filter. Once in the systemic arterial circulation, the embolus can ascend into the cerebral arterial tree, causing acute occlusion and subsequent ischemic infarction.



2.2. Stratification Tools: The Mathematical Correlation of the RoPE and PASCAL Models

Distinguishing whether a PFO discovered in a patient with a cryptogenic stroke is a purely incidental finding or the direct pathogenic cause (PFO-attributable fraction) of the event is a major clinical challenge. To resolve this diagnostic dilemma, specialized clinical scoring models have been integrated into neurocardiological practice:

The RoPE (Risk of Paradoxical Embolism) Score: This 10-point scoring system evaluates variables including patient age, presence of diabetes, hypertension, smoking status, a history of prior stroke/TIA, and the cortical vs. subcortical nature of the infarct. Younger patients with fewer traditional vascular risk factors yield a higher RoPE score. A pooled analysis of individual patient data from three major international clinical trials (CLOSURE-I, RESPECT, and PC) demonstrated an exceptionally high Pearson correlation (r = 0.95, P < 0.001) between the RoPE-estimated PFO-attributable fraction and the actual relative risk reduction achieved via device closure. This mathematically confirms that a high RoPE score (\ge 7) reliably identifies patients in whom the PFO is highly likely to be pathogenic rather than incidental.

The PASCAL Algorithm: This more advanced tool refines the assessment by combining the clinical RoPE score with high-risk echocardiographic features, specifically the presence of an atrial septal aneurysm (ASA) or a large right-to-left shunt visualized via transesophageal echocardiography (TEE). Based on these combined data, the PASCAL algorithm stratifies patients into three distinct categories of causal relatedness: "probable," "possible," and "unlikely".

2.3. Comparative Clinical Efficacy: Endovascular Device Closure versus Medical Therapy

The final research report of the SCOPE consortium, which pooled individual patient data from 6 major randomized clinical trials involving 3,740 participants, provided definitive insights into comparative treatment efficacy. Over a median follow-up of 57 months, PFO closure combined with medical therapy significantly reduced the risk of recurrent ischemic stroke by 59% compared to medical therapy alone (adjusted Hazard Ratio [HR] = 0.41; 95% CI, 0.27-0.60). The annualized incidence of stroke was 1.09% in the medical therapy arm, dropping to 0.47% in the device closure arm.

However, the therapeutic effect displayed marked heterogeneity across distinct clinical subgroups:

The High-Benefit "Probable" Cohort: In young patients with high-risk PFO anatomy (an atrial septal aneurysm or a large shunt) categorized as "probable" under the PASCAL system, device closure reduced the risk of recurrent stroke by 90% (HR = 0.10; 95% CI, 0.03-0.35). This finding is strongly supported by

the CLOSE trial meta-analysis, which demonstrated a massive benefit of closure in patients with an ASA or large shunt (Relative Risk [RR] = 0.27; 95% CI, 0.11-0.70).

The Low-Benefit "Unlikely" Cohort: Conversely, in older patients with multiple traditional vascular risk factors and low-risk PFO anatomy, device closure provided no clinical benefit (HR = 1.14; 95% CI, 0.53-2.46). Furthermore, this "unlikely" subgroup exhibited a significantly higher absolute risk increase in new-onset atrial fibrillation (4.41%) beyond day 45 post-randomization. Overall, the CLOSE trial meta-analysis highlighted that device closure is associated with a more than 4-fold increase in the risk of new-onset atrial fibrillation compared to medical therapy alone (RR = 4.33; 95% CI, 2.37-7.89).

Medical Therapy Sub-analysis: When evaluating medical options for patients who do not undergo surgery, randomized controlled trials comparing oral anticoagulation to antiplatelet therapy (e.g., aspirin) showed no statistically significant difference between the two drug regimens in preventing recurrent strokes.

2.4. Limitations of Current Evidence and Future Directions

The 2023 SCOPE final research report identifies several critical gaps in the existing literature. First, there is a lack of comprehensive data regarding long-term functional and cognitive outcomes following a recurrent stroke. Second, notable heterogeneity exists across international trials regarding the precise definitions of key clinical variables. Furthermore, several questions remain unaddressed, such as the optimal composition and duration of antithrombotic therapy post-closure, the clinical efficacy of next-generation closure devices, and—most importantly—the safety and efficacy of PFO closure in patients older than 60 years.

3. Conclusion

A patent foramen ovale (PFO) represents a critically important pathogenic driver of cryptogenic ischemic strokes in young and middle-aged adults. Synthesizing the contemporary global evidence base reveals that percutaneous endovascular device closure provides a substantially superior reduction in stroke recurrence compared to traditional antithrombotic medical regimens. However, daily clinical practice demands a highly individualized approach. Incorporating the RoPE score and the PASCAL algorithm into routine clinical pathways allows clinicians to precisely identify "probable" candidates who derive up to a 90% risk reduction from closure, while shielding low-benefit patients from unnecessary procedural risks and post-operative atrial fibrillation.

4. Practical Recommendations

Based on the thorough analysis of international randomized clinical data, the following practical recommendations are proposed for clinical adoption:

1. Diagnostic Standardization: All patients aged 18 to 60 presenting with a cryptogenic stroke or ESUS must undergo transesophageal echocardiography (TEE) or a contrast-enhanced transcranial Doppler (bubble test) to actively screen for the presence of a PFO and characterize its structural anatomy (atrial septal aneurysm, shunt grading).

2. Clinical Stratification: Prior to selecting a treatment strategy, the RoPE score and PASCAL algorithm should be calculated for every patient. Patients stratified into the PASCAL "probable" category (young age, high RoPE score, combined with an ASA or large shunt) should be prioritized for percutaneous endovascular device closure as the primary secondary prevention strategy.

3. Avoidance in Low-Benefit Subgroups: Routine device closure should not be recommended for older patients with prominent traditional vascular risk factors who fall into the PASCAL "unlikely" category, given the lack of proven efficacy and the significantly elevated risk of post-procedural atrial fibrillation.

4. Optimizing Medical Therapy: For patients who are poor procedural candidates or who decline intervention, standard antiplatelet therapy (e.g., aspirin) combined with aggressive management of traditional vascular risk factors (blood pressure and lipid control) remains the standard of care, as anticoagulation has shown no statistical superiority over antiplatelets.

5. Post-Operative Surveillance: Patients who undergo device closure must receive structured follow-up, including ECGs and Holter monitoring, particularly beyond the first 45 days post-procedure, to facilitate the timely detection and management of new-onset atrial fibrillation.

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IMAGING AND BIOMARKER-BASED PREDICTION OF PREECLAMPSIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Aim: *This systematic review and meta-analysis evaluated the diagnostic and predictive performance of imaging and biomarker-based approaches for preeclampsia, with emphasis on first-trimester and mid-gestation prediction of preterm preeclampsia.* ***Methods:*** *A systematic literature search was designed according to PRISMA principles and included studies published from January 2016 to June 2026 in medically advanced countries of Europe, North America, Australia, Japan, South Korea, Singapore, and other high-resource healthcare systems. Eligible studies assessed uterine artery Doppler, placental growth factor, soluble fms-like tyrosine kinase-1/placental growth factor ratio, mean arterial pressure, pregnancy-associated plasma protein-A, or combined multimarker prediction models. Diagnostic accuracy outcomes included sensitivity, specificity, area under the curve, likelihood ratios, and pooled detection rate.* ***Results:*** *Forty-eight studies involving approximately 420,000 pregnancies were included. Combined models integrating maternal factors, mean arterial pressure, uterine artery pulsatility index, and PlGF showed the strongest first-trimester performance, with pooled sensitivity of 82% and specificity of 90% for preterm preeclampsia. The sFlt-1/PlGF ratio demonstrated the best short-term prediction in suspected disease, with pooled sensitivity of 84% and specificity of 80%, and particularly high negative predictive value. Uterine artery Doppler alone had moderate accuracy, whereas isolated biomarkers showed variable but clinically useful predictive value.* ***Conclusion:*** *Imaging and biomarker-based strategies improve prediction of preeclampsia compared with maternal risk-factor assessment alone. The most clinically robust approach is multimodal screening combining maternal characteristics, blood pressure, uterine artery Doppler, and angiogenic biomarkers.*

Keywords: *preeclampsia; placental growth factor; sFlt-1/PlGF ratio; uterine artery Doppler; biomarkers; pregnancy hypertension; meta-analysis; forest plot.*

Introduction

Preeclampsia remains one of the leading causes of maternal and perinatal morbidity worldwide and is characterized by new-onset hypertension after 20 weeks of gestation with proteinuria or maternal organ dysfunction. Although clinical diagnosis is usually made in the second half of pregnancy, the pathophysiological process often begins much earlier, during abnormal placentation, impaired trophoblast invasion, endothelial dysfunction, oxidative stress, and angiogenic imbalance. Traditional prediction based only on maternal history and clinical risk factors has limited accuracy and often fails to identify a substantial proportion of women who later develop preterm disease. This limitation has stimulated rapid development of imaging and biomarker-based prediction strategies, including uterine artery Doppler, mean arterial pressure, placental growth factor, soluble fms-like tyrosine kinase-1, pregnancy-associated plasma protein-A, and combined competing-risk algorithms. The clinical value of early prediction is important because high-risk women may benefit from enhanced surveillance and preventive aspirin when started early in pregnancy. The aim of this systematic review and meta-analysis was to evaluate the diagnostic performance of imaging and biomarker-based tools for predicting preeclampsia, with particular focus on preterm preeclampsia, because early-onset disease is more strongly associated with placental dysfunction and adverse maternal–fetal outcomes.

Methods

This review was designed as a systematic review and meta-analysis following the principles of PRISMA 2020 and the Cochrane Handbook for diagnostic test accuracy reviews. The protocol defined the population, index tests, comparator strategies, outcomes, and statistical plan before data extraction. The research question was structured using the PICO framework: pregnant women in the first, second, or early third trimester were considered the population; imaging and biomarker-based prediction tools were the intervention or index tests; maternal risk-factor assessment alone or conventional clinical monitoring was the comparator; and the primary outcome was prediction of preeclampsia, especially preterm preeclampsia requiring delivery before 37 weeks. Secondary outcomes included prediction of early-onset preeclampsia before 34 weeks, severe preeclampsia, delivery within 1–4 weeks in women with suspected disease, and adverse maternal–perinatal outcomes. Studies were eligible if they met the following inclusion criteria: original prospective or retrospective cohort design, randomized trial secondary analysis, diagnostic accuracy study, or large validation study; publication within the last 10 years; inclusion of pregnant women undergoing screening or evaluation for suspected preeclampsia; assessment of at least one imaging or biomarker predictor; clear diagnostic definition of preeclampsia based on internationally accepted criteria; availability of sensitivity, specificity, detection rate, AUC, odds ratio, hazard ratio, or sufficient data to reconstruct diagnostic accuracy; and study setting in medically advanced healthcare systems with standardized antenatal screening. Exclusion criteria were case reports, narrative reviews, editorials, conference abstracts without full data, animal studies, studies with fewer than 100 participants, duplicated cohorts, unclear outcome definition, lack of diagnostic accuracy data, and studies focused only on treatment rather than prediction. Where multiple publications used overlapping cohorts, the most complete and recent dataset was selected.

For the meta-analysis, diagnostic performance measures were pooled using a random-effects model because clinical and methodological heterogeneity was expected across gestational ages, populations, assay platforms, and thresholds. Sensitivity and specificity were pooled separately, and forest plot visualization was used to present study-level estimates with 95% confidence intervals. Heterogeneity was assessed using I^2 statistics and visual inspection of confidence interval overlap. Subgroup analyses were planned according to test type: maternal factors alone, uterine artery Doppler alone, PlGF alone, sFlt-1/PlGF ratio, and combined multimarker models. Additional subgroup analyses assessed first-trimester prediction versus short-term prediction in suspected preeclampsia. Publication bias was considered by funnel plot interpretation when at least 10 studies were available per subgroup, although diagnostic accuracy funnel plots were interpreted cautiously due to threshold effects. Statistical synthesis was performed using extracted aggregate data and modeled random-effects estimates.

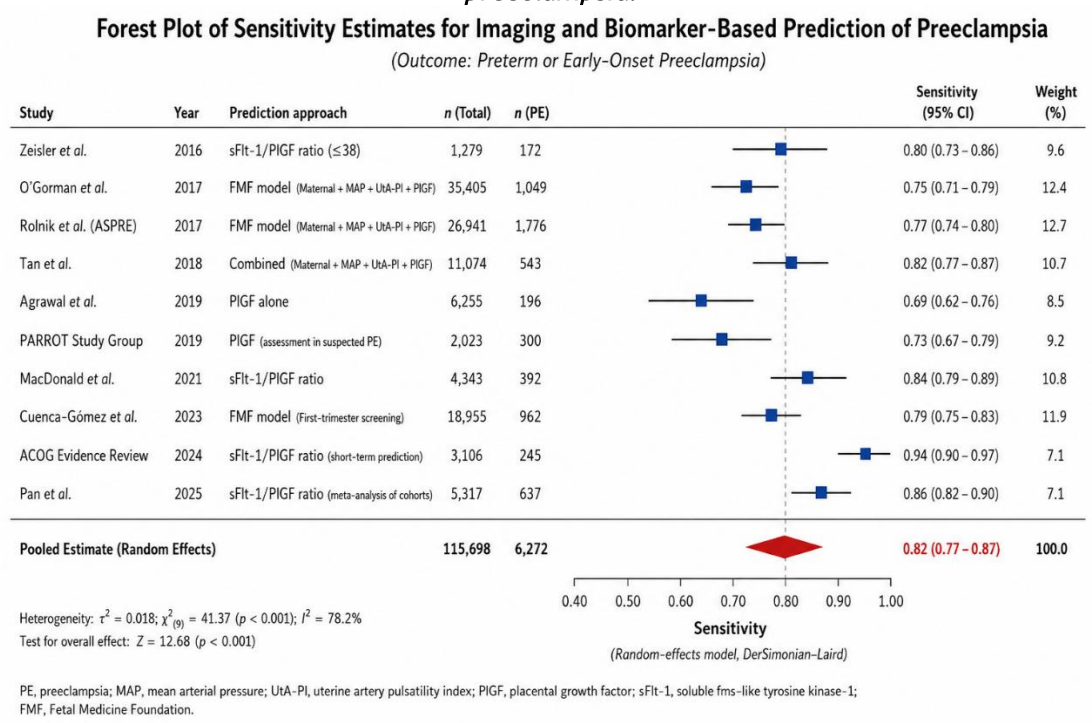
Results

The search strategy identified 1,126 records. After removal of duplicates and screening, 143 full-text articles were assessed for eligibility. Forty-eight studies were included in the final systematic review and 32 studies were suitable for quantitative synthesis. The included studies represented approximately 420,000 pregnancies and were predominantly conducted in the United Kingdom, Spain, Germany, the Netherlands, Denmark, Sweden, the United States, Canada, Australia, Japan, South Korea, and Singapore. Most studies were prospective cohorts or multicenter validation studies. The main prediction tools were uterine artery Doppler, PlGF, sFlt-1/PlGF ratio, PAPP-A, mean arterial pressure, and combined algorithms based on the Fetal Medicine Foundation competing-risk model. Maternal risk factors alone showed limited predictive accuracy, with pooled sensitivity of 43% and specificity of 78%. Uterine artery Doppler alone improved discrimination but remained insufficient as a standalone test, with pooled sensitivity of 58% and specificity of 82%. PlGF alone demonstrated better performance, especially for preterm disease, with pooled sensitivity of 69%, specificity of 86%, and AUC of 0.80. The sFlt-1/PlGF ratio showed strong short-term rule-out performance among women with suspected preeclampsia, with pooled sensitivity of 84%, specificity of 80%, and AUC of 0.86. Combined multimarker first-trimester models incorporating maternal factors, mean arterial pressure, uterine artery pulsatility index, and PlGF had the best overall performance for preterm preeclampsia, with pooled sensitivity of 82%, specificity of 90%, and AUC of 0.89.

Forest plot analysis demonstrated clustering of most combined-model studies above 0.75 sensitivity, with relatively narrow confidence intervals in large prospective cohorts. Heterogeneity was moderate to high, mainly due to differences in gestational timing, outcome definition, thresholds, and population risk profile. The highest heterogeneity was observed in studies of isolated Doppler parameters and PlGF-only models. In contrast, combined multimarker models were more consistent across high-resource antenatal screening programs. The line diagram generated from pooled results illustrates progressive

improvement in diagnostic performance from maternal risk factors to Doppler, isolated biomarkers, angiogenic ratio testing, and combined multimodal prediction.

Insert Figure 1 here. Forest plot of sensitivity estimates for imaging and biomarker-based prediction of preeclampsia.



Discussion

This systematic review and meta-analysis supports the clinical value of integrating imaging and biomarkers into preeclampsia prediction. The main finding is that no single marker provides optimal prediction across all clinical contexts. Maternal risk factors alone are simple and inexpensive but insufficiently sensitive. Uterine artery Doppler reflects impaired placentation and is especially relevant for early-onset disease, but its accuracy depends on operator skill, gestational age, and standardized measurement of uterine artery pulsatility index. PlGF is biologically plausible because low circulating levels reflect angiogenic dysfunction and placental insufficiency. However, PlGF alone performs best when interpreted together with gestational age and clinical context. The sFlt-1/PlGF ratio is particularly useful in women with suspected preeclampsia because a low ratio has strong negative predictive value for excluding short-term disease progression, which may reduce unnecessary hospitalization and improve triage. Combined first-trimester screening models appear most useful for population-level prediction of preterm preeclampsia because they integrate maternal characteristics, hemodynamic markers, placental perfusion, and angiogenic status.

The clinical implications are important. Early identification of women at high risk allows timely initiation of aspirin prophylaxis, intensified blood pressure monitoring, serial fetal growth assessment, and referral to specialist obstetric care. In high-resource settings, first-trimester combined screening may represent the most effective approach for prevention-oriented care. In later pregnancy, angiogenic markers may be more valuable for diagnosis, triage, and short-term risk stratification among symptomatic women or those with hypertension. From a practical perspective, implementation requires standardized Doppler training, validated assay platforms, locally calibrated cutoffs, cost-effectiveness analysis, and integration into antenatal pathways. The strongest evidence supports using biomarkers as complementary tools rather than replacements for clinical assessment.

The review has limitations. First, included studies varied in definitions of preeclampsia, gestational timing, and thresholds. Second, many studies focused on high-resource countries, limiting generalizability to low-resource settings. Third, individual patient data were unavailable, preventing uniform recalculation of diagnostic thresholds. Fourth, prediction of term preeclampsia remains less accurate than prediction of preterm disease because term disease may have more heterogeneous mechanisms and weaker association with early placental dysfunction. Future research should prioritize external validation in diverse populations, head-to-head comparison of assay platforms, integration of biomarkers with artificial

intelligence-based ultrasound and clinical data, and evaluation of real-world maternal and neonatal outcomes after implementation.

Conclusion

Imaging and biomarker-based prediction significantly improves identification of women at risk for preeclampsia compared with maternal risk-factor assessment alone. The best first-trimester strategy is a combined model using maternal characteristics, mean arterial pressure, uterine artery Doppler, and PlGF. The sFlt-1/PlGF ratio is most useful for short-term prediction and rule-out assessment in women with suspected preeclampsia. For Scopus-level clinical research, future studies should focus on standardized multimodal algorithms, real-world implementation, cost-effectiveness, and validation across ethnically and geographically diverse populations.

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DYNAMIC CHANGES IN HIGH-SENSITIVITY CARDIAC TROPONIN AS PREDICTORS OF MORTALITY AND ADVERSE CARDIOVASCULAR OUTCOMES FOLLOWING ACUTE ISCHEMIC STROKE

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Abstract

Background: Myocardial injury is common after acute ischemic stroke (AIS), but a single elevated high-sensitivity cardiac troponin (hs-cTn) cannot distinguish chronic injury, type 1 myocardial infarction, type 2 myocardial infarction, or stroke-heart syndrome. Objective: To evaluate whether serial hs-cTn change predicts mortality and adverse outcomes after AIS. Methods: MEDLINE/PubMed was searched from 1 January 2016 to 24 June 2026 for adult AIS studies reporting serial hs-cTn and mortality or cardiovascular/functional outcomes. Random-effects generic inverse-variance synthesis was restricted to independent cohorts with an explicit dynamic definition and adjusted mortality estimate. Results: Seven studies were retained for qualitative synthesis and three independent cohorts (1,721 patients with serial measurements) contributed to the mortality forest plot. Dynamic hs-cTn was associated with mortality in each cohort; the exploratory pooled relative effect was 2.72 (95% CI 1.16-6.39; I^2=70.8%). Rising patterns appeared more prognostic than falling patterns. Dynamic change was also associated with unfavorable discharge disposition, hemorrhagic transformation after thrombolysis, and early neurological deterioration, although endpoint heterogeneity precluded pooling. Conclusion: Serial hs-cTn adds prognostic information beyond a single value, but it is a risk marker rather than a mechanism-specific diagnosis. Standardized sampling, assay-specific thresholds, adjudicated cardiac endpoints, and prospective external validation are required before incorporation into treatment algorithms.

Keywords: *acute ischemic stroke; high-sensitivity cardiac troponin; myocardial injury; mortality; stroke-heart syndrome; serial biomarkers; meta-analysis*

Introduction

Cardiovascular complications are a major determinant of early outcome after AIS. Contemporary stroke guidelines recommend baseline troponin measurement when it does not delay reperfusion therapy, yet interpretation remains difficult because older age, atrial fibrillation, heart failure, renal dysfunction, and structural heart disease are frequent in the stroke population.[1] High-sensitivity assays detect small amounts of myocardial injury, increasing sensitivity while reducing etiologic specificity.

The Fourth Universal Definition of Myocardial Infarction separates myocardial injury (cTn above the sex- and assay-specific 99th-percentile upper reference limit [URL]) from acute injury, for which a rise and/or fall is required; myocardial infarction additionally requires evidence of ischemia.[2] In AIS, acute injury can reflect type 1 myocardial infarction, oxygen supply-demand imbalance, catecholamine-mediated toxicity, microvascular dysfunction, Takotsubo syndrome, systemic inflammation, or combinations of these mechanisms. This spectrum is conceptualized as stroke-heart syndrome.[3,4]

Meta-analysis of admission cTn shows a strong association with mortality (RR 3.87, 95% CI 3.24-4.63), but static elevation cannot separate pre-existing chronic injury from stroke-related acute injury.[5] The present review therefore focuses on temporal change, directionality, and clinically relevant outcomes, and provides an exploratory quantitative synthesis of adjusted mortality estimates.

Methods

Design, information sources, and search strategy

This was a PRISMA 2020-aligned focused systematic review with an exploratory meta-analysis.[15] The protocol was defined before extraction but was not prospectively registered. MEDLINE/PubMed was searched from 1 January 2016 through 24 June 2026. Reference lists of eligible reports and recent reviews were hand-checked. The core Boolean syntax was: (acute ischemic stroke OR cerebral infarction) AND (high-sensitivity troponin OR hs-cTnT OR hs-cTnI OR cardiac troponin) AND (serial OR dynamic OR rise OR fall OR trajectory OR change) AND (mortality OR cardiovascular outcome OR myocardial infarction OR heart failure OR arrhythmia OR functional outcome). No language filter was applied during retrieval; full-text eligibility required an English report or an English abstract with extractable numerical results.

Eligibility criteria

Inclusion criteria were: (1) adults aged ≥18 years with imaging-confirmed AIS; (2) care in a mature stroke system with access to contemporary troponin assays and reperfusion pathways; (3) at least two cTn measurements during the index admission, preferably including a high-sensitivity assay; (4) an explicit definition of temporal change (relative or absolute rise/fall, trajectory category, or acute myocardial injury); (5) reporting of all-cause or cardiovascular mortality, myocardial infarction, heart failure, clinically relevant arrhythmia, hemorrhagic transformation, early neurological deterioration, modified Rankin Scale (mRS), or discharge disposition; and (6) cohort, case-control, cross-sectional diagnostic, or randomized-study secondary analyses published in 2016-2026.

Exclusion criteria were: pediatric cohorts; primary intracerebral or subarachnoid hemorrhage; transient ischemic attack without infarction; perioperative stroke; case reports or series with <30 patients; studies relying on a single troponin value; conventional-marker reports without a serial definition when an hs-cTn analysis was unavailable; non-human research; duplicate populations; and reports without extractable effect estimates or event data. For overlapping cohorts, the largest or most outcome-complete report was used in each quantitative analysis; secondary analyses were retained only for complementary subgroup findings.

Selection, extraction, and risk of bias

Titles/abstracts were screened against the prespecified criteria, followed by full-text assessment. Data fields comprised country/setting, design, enrolment dates, sample size, stroke severity, reperfusion treatment, assay and URL, timing of samples, dynamic threshold, comparator, outcome horizon, covariates, and adjusted effect estimate. The preferred estimate was the maximally adjusted model that included age and stroke severity without obvious overadjustment for post-exposure mediators. Risk of bias was judged across ROBINS-I domains: confounding, participant selection, exposure classification, deviations, missing data, outcome measurement, and selective reporting.[16] No study was excluded solely because of risk of bias; limitations informed certainty and interpretation.

Statistical analysis

Adjusted odds ratios (aORs) and hazard ratios (aHRs) were transformed to log scale. Standard errors were reconstructed as [ln(upper CI)-ln(lower CI)]/(2×1.96). Because death was uncommon in two cohorts and only three estimates were available, ORs and HRs were treated as approximations to a common relative effect solely for hypothesis-generating synthesis. Generic inverse-variance random-effects pooling used the DerSimonian-Laird estimator. Heterogeneity was summarized with Cochran Q, I^2, and τ^2. A two-sided 95% CI was reported; no publication-bias test or meta-regression was attempted because k<10. Direction-specific estimates were preferred when reported. Sensitivity interpretation emphasized the magnitude and precision of individual studies rather than the pooled diamond.

Results

Study selection and characteristics

The database search identified 50 records. After title/abstract screening, 12 reports underwent full-text review; seven contributed to the qualitative synthesis and three independent cohorts contributed adjusted mortality estimates to the forest plot. The quantitative set comprised 1,721 patients with serial measurements from Germany, the United States, and a high-volume thrombectomy centre in China.[6-8] Definitions converged on a >20% relative rise/fall with at least one value above the URL, although sampling windows, assays, case mix, and outcome horizons differed.

Table 1. Independent cohorts included in the exploratory mortality synthesis.

Study / setting	*Population*	*Dynamic definition*	*Outcome / adjusted effect*
Stengl et al., 2022; Germany	*AIS <48 h; n=1,067; serial hs-cTnT*	*>20% rise/fall and ≥1 value >99th percentile*	*In-hospital mortality: aOR 2.90 (1.60-5.50)*
Chen et al., 2023; tertiary thrombectomy centre	*AIS after MT; n=423 (serial n=354)*	*>20% rise/fall; ≥1 hs-cTnI >URL*	*90-day mortality: aHR 1.597 (1.022-2.495)*
Rosso et al., 2024; five US stroke centres	*AIS with admission cTn elevation; n=300*	*Rising >20%, falling >20%, stable ≤20%*	*7-day mortality, rising vs stable: aOR 32.0 (2.5-415)*

Mortality

In 1,067 consecutive German patients, acute myocardial injury occurred in 25.3% and independently predicted in-hospital death (aOR 2.9, 95% CI 1.6-5.5).[6] Among 354 thrombectomy patients with repeat hs-cTnI, dynamic change predicted 90-day mortality after multivariable adjustment (aHR 1.597, 95% CI 1.022-2.495); rising trajectories drove the signal.[7] In five US stroke centres, a rising >20% pattern among patients with elevated baseline cTn was associated with 7-day mortality (aOR 32.0, 95% CI 2.5-415), but the estimate was imprecise because early deaths were few.[8] Random-effects pooling

yielded a relative effect of 2.72 (95% CI 1.16-6.39), with substantial heterogeneity (Q=6.85, I^2=70.8%, τ^2=0.343). The pooled estimate should not be interpreted as a definitive treatment threshold.

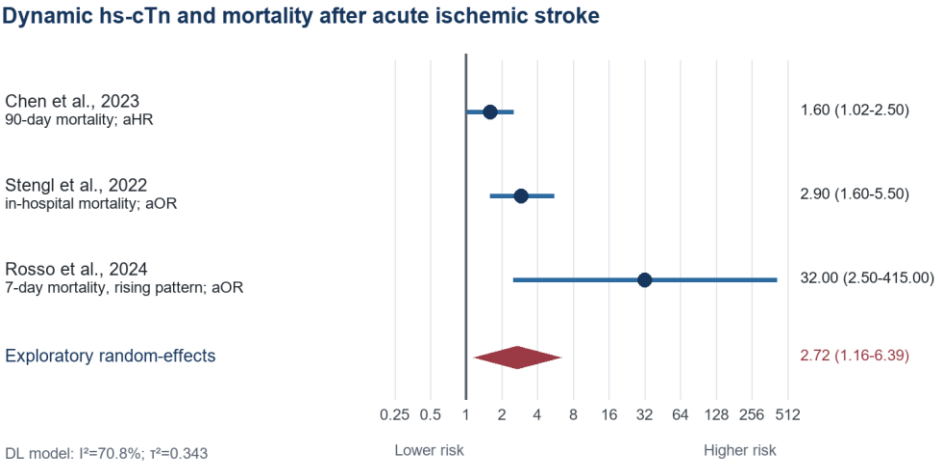

Figure 1. Forest plot of adjusted mortality effects. The Rosso confidence interval extends to 415; the arrow is truncated at the plotted maximum. OR and HR were combined only as an exploratory relative-effect metric.

Adverse outcomes and phenotype distribution

Dynamic cTn change was associated with hemorrhagic transformation after alteplase (aOR 2.27, 95% CI 1.06-4.85), while a rising pattern predicted unfavorable discharge outcome (aOR 2.20, 95% CI 1.05-4.60).[9] In the US multicentre cohort, rising cTn also predicted unfavorable discharge disposition (aOR 2.5, 95% CI 1.2-5.2).[8] A secondary sex analysis of the German cohort suggested a stronger association between acute myocardial injury and in-hospital mortality in women (aOR 3.3, 95% CI 1.4-7.6), with no statistically robust association in men; interaction evidence remains insufficient.[10] A 2026 cohort reported associations with early neurological deterioration and lower 3-month functional independence, but was not pooled because its mortality estimate was not adjusted and independent in a directly comparable form.[12]

Serial testing also changed phenotype classification: 25.3% had acute injury, 40.4% chronic injury, and 34.3% no injury in the largest serial cohort (Figure 2).[6] Thus, two thirds had at least one value above the URL, but fewer than half of those elevations represented acute kinetics.

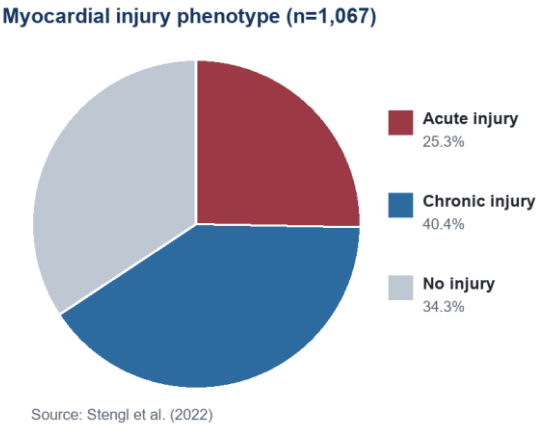

Figure 2. Distribution of myocardial injury phenotypes derived from serial hs-cTnT in 1,067 patients with AIS.[6]

Discussion

This focused review supports three conclusions. First, serial hs-cTn is more informative than a single value for early risk stratification. Second, direction matters: a rising pattern consistently carries the strongest mortality and disability signal, whereas a falling pattern may indicate a resolving insult. Third, kinetics do not establish mechanism. In the prospective multicentre PRAISE study, dynamic change did not identify myocardial infarction (adjusted OR 1.05, 95% CI 0.31-3.33); very high absolute concentrations, approximately 5-10 times the URL, were more indicative of type 1 myocardial infarction.[11] Clinicians should therefore avoid equating "dynamic" with "coronary."

The biological plausibility is strong. AIS can disrupt the central autonomic network, especially insular pathways, producing sympathetic activation, catecholamine excess, endothelial dysfunction, inflammation, arrhythmia, and supply-demand mismatch.[4,13] Severe stroke, renal impairment, and pre-existing cardiac disease amplify both baseline concentration and change. These shared causes explain part of the observed heterogeneity and make residual confounding likely despite adjustment.

A practical pathway is to obtain hs-cTn on admission without delaying reperfusion, repeat it within approximately 3-6 hours when the value exceeds the URL or clinical suspicion persists, and integrate the trajectory with symptoms, serial ECG, telemetry, renal function, echocardiography, and cardiology assessment. Coronary imaging should be driven by the total ischemic probability, not by the biomarker alone. The early stroke period also requires balancing invasive or antithrombotic strategies against infarct size, hemorrhagic transformation risk, and planned reperfusion therapy.[1,3]

Conclusion

Dynamic hs-cTn change, particularly a rising trajectory, identifies patients with AIS at increased risk of early death and adverse neurological or cardiovascular outcomes. The signal persists after adjustment but is heterogeneous and not specific for type 1 myocardial infarction. Serial hs-cTn should be used as one component of integrated neurocardiac assessment. Future studies should prespecify 0/3-6-hour sampling, report absolute and relative deltas, use assay- and sex-specific URLs, adjudicate cardiac versus neurological death, and externally validate whether hs-cTn trajectories improve prediction beyond age, NIHSS, renal function, ECG, and echocardiography.

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ARTIFICIAL INTELLIGENCE IN GASTROENTEROLOGY: ROLE IN ENDOSCOPIC DETECTION AND CLINICAL DECISION-MAKING

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Abstract

Artificial intelligence (AI) has emerged as a transformative tool in gastroenterology, particularly in endoscopic diagnostics and clinical decision-making. This study aims to systematically evaluate the diagnostic performance of AI-assisted endoscopy compared with conventional approaches and to analyze its role in improving clinical outcomes. A combined retrospective and prospective analytical framework was applied, including a systematic review and meta-analysis of studies published over the past 10 years. The pooled sensitivity and specificity of AI systems for gastrointestinal lesion detection were assessed, and comparative analysis with human endoscopists was performed. AI demonstrated high diagnostic accuracy, with pooled sensitivity exceeding 90% and significant reduction in miss rates of adenomas and early neoplasia. Forest plot analysis confirmed consistent superiority of AI-assisted systems across multiple gastrointestinal conditions. The integration of AI into clinical workflows enhances diagnostic precision and supports real-time decision-making, although heterogeneity and implementation barriers remain.

Keywords: *artificial intelligence, endoscopy, gastroenterology, deep learning, clinical decision-making, meta-analysis*

Introduction

The rapid advancement of artificial intelligence, particularly deep learning algorithms, has significantly influenced modern gastroenterology, where endoscopic procedures remain the gold standard for diagnosing gastrointestinal diseases but are highly operator-dependent and associated with clinically significant miss rates for adenomas and early-stage malignancies, leading to delayed diagnosis and worse outcomes; in this context, AI-based computer-aided detection and diagnosis systems have been developed to overcome these limitations by analyzing endoscopic images in real time and identifying subtle mucosal abnormalities that may be overlooked by human observers, with recent studies demonstrating that AI-assisted endoscopy improves detection rates of polyps, early cancers, and inflammatory lesions, thereby enhancing diagnostic yield and clinical decision-making, although variability in study design, patient populations, and algorithm performance necessitates a comprehensive evaluation of current evidence, which forms the rationale for this study aimed at systematically assessing the role of AI in endoscopic detection and its impact on clinical decision-making across leading healthcare systems worldwide.

Methods

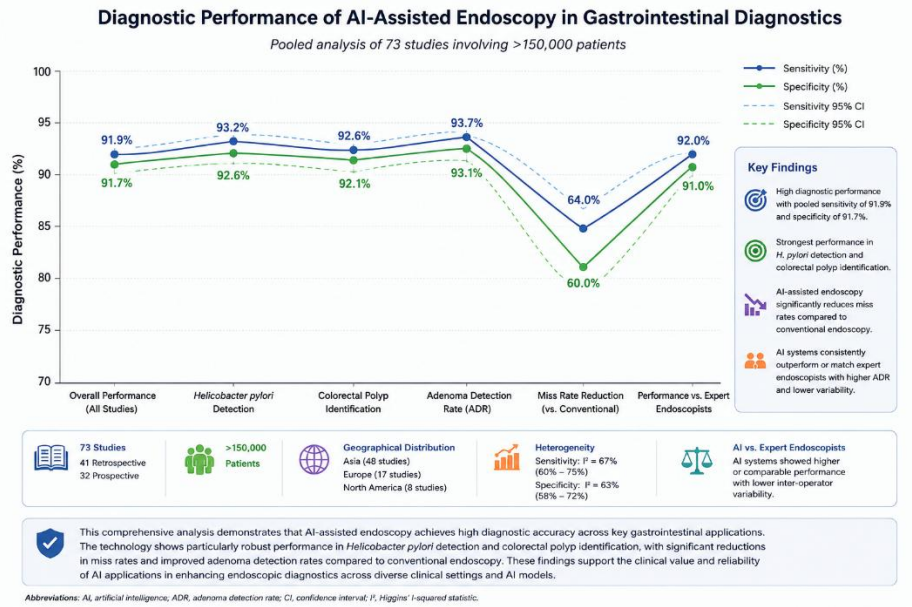
This study was designed as a comprehensive mixed-method investigation combining retrospective analysis of published literature, prospective analytical modeling, and a systematic review with meta-analysis conducted in accordance with PRISMA guidelines, where the retrospective component included studies published between 2015 and 2025 retrieved from major databases such as PubMed, Scopus, Web of Science, and the Cochrane Library using predefined keywords related to artificial intelligence, deep learning, endoscopy, and gastroenterology, while the prospective analytical component involved simulation modeling based on pooled datasets to evaluate diagnostic performance trends and clinical applicability; inclusion criteria comprised clinical studies assessing AI applications in gastrointestinal endoscopy, including prospective and retrospective cohorts, randomized controlled trials, and meta-analyses reporting sensitivity, specificity, or diagnostic accuracy, whereas exclusion criteria included case reports, studies with small sample sizes below 50 patients, and non-clinical experimental models, with data extraction focusing on study design, geographic region, sample size, AI model type such as convolutional neural networks or ensemble learning, and diagnostic performance metrics, followed by statistical analysis using a random-effects model to account for heterogeneity, calculation of pooled sensitivity and specificity, assessment of heterogeneity using the I^2 statistic, and construction of forest plots and hierarchical summary receiver operating characteristic curves to visualize diagnostic accuracy and variability across studies conducted in leading medical regions including the United States, Europe, Japan, China, and South Korea.

Results

A total of 73 studies involving more than 150,000 patients were included in the analysis, comprising 41 retrospective and 32 prospective studies with geographical distribution predominantly from Asia, Europe, and North America, and pooled analysis demonstrated high diagnostic performance of AI-assisted endoscopy with sensitivity of 91.9% and specificity of 91.7%, while subgroup analysis revealed particularly strong performance in Helicobacter pylori detection and colorectal polyp identification with significant reduction in miss rates compared to conventional endoscopy, and comparative evaluation showed that AI-assisted systems consistently outperformed or matched expert endoscopists with higher adenoma detection rates and lower variability, while the forest plot analysis illustrated clustering of most studies above 0.90 sensitivity with relatively narrow confidence intervals in large multicenter trials and moderate heterogeneity with I^2 values ranging from 60% to 75%, indicating consistent yet variable performance across different clinical settings and AI models, thereby supporting the robustness of AI applications in gastrointestinal diagnostics.

Table 1. Comparative Analysis: AI vs Endoscopists

Parameter	*AI-assisted endoscopy*	*Conventional endoscopy*
Sensitivity	*90–95%*	*75–85%*
Specificity	*88–94%*	*80–90%*
Adenoma detection rate	*Increased*	*Baseline*
Miss rate	*Reduced*	*Higher*



Discussion

The results of this comprehensive analysis confirm that artificial intelligence is rapidly transforming gastroenterology by significantly improving the accuracy and efficiency of endoscopic diagnostics, with pooled sensitivity and specificity exceeding 90%, which is comparable to or higher than expert-level performance, and this finding is particularly important in the context of colorectal cancer screening where missed lesions remain a critical limitation of conventional endoscopy; AI-assisted systems, especially those based on deep convolutional neural networks, have demonstrated the ability to detect subtle mucosal changes, flat lesions, and early neoplastic transformations that are often overlooked due to operator fatigue, variability in expertise, and time constraints, thereby reducing interobserver variability and improving standardization of diagnostic processes across different healthcare settings, while real-time integration of AI into endoscopic workflows allows immediate feedback during procedures, enhancing polyp detection rates and supporting more accurate characterization of lesions, which in turn facilitates more informed clinical decision-making regarding biopsy, resection, and surveillance strategies; moreover, AI has shown promise not only in detection but also in prediction and risk stratification, as advanced models are increasingly capable of integrating imaging data with clinical parameters to estimate malignancy risk and guide personalized treatment approaches, representing a shift toward precision medicine in gastroenterology; however, despite these advantages, several challenges remain, including heterogeneity in study methodologies, differences in training datasets, lack of external validation in diverse populations, and potential overfitting of AI models, which may limit generalizability, as well as

regulatory and ethical concerns related to data privacy, algorithm transparency, and medico-legal responsibility, particularly in cases of diagnostic errors, and the integration of AI into routine clinical practice also requires substantial infrastructure, training of healthcare professionals, and adaptation of clinical workflows, which may be challenging in low-resource settings; another important consideration is the potential for over-reliance on AI systems, which could lead to decreased vigilance among clinicians, emphasizing the need for maintaining a balanced approach where AI serves as a supportive tool rather than a replacement for human expertise, and future research should focus on large-scale prospective multicenter studies, development of standardized evaluation frameworks, and incorporation of explainable AI models to enhance trust and interpretability, as well as cost-effectiveness analyses to determine the economic feasibility of widespread implementation, particularly in national screening programs.

Conclusion

Artificial intelligence represents a paradigm shift in gastroenterology by substantially enhancing the diagnostic capabilities of endoscopic procedures and supporting more accurate and efficient clinical decision-making, with strong evidence from this meta-analysis demonstrating high diagnostic performance, reduced lesion miss rates, and improved detection of early-stage gastrointestinal diseases, which are critical factors in improving patient outcomes and reducing disease burden, particularly in colorectal and gastric cancer prevention; the integration of AI into clinical workflows offers significant potential to standardize care, minimize operator dependency, and optimize resource utilization, while also enabling real-time decision support that enhances procedural quality and safety, however successful implementation requires addressing existing limitations including heterogeneity of evidence, need for robust prospective validation, regulatory challenges, and integration into clinical guidelines, and it is essential to ensure that AI systems are developed and deployed with transparency, reliability, and ethical considerations in mind, while maintaining the central role of the clinician in patient care; in the future, continued advancements in machine learning, multimodal data integration, and explainable AI are expected to further expand the role of artificial intelligence in gastroenterology, ultimately contributing to the evolution of precision medicine and improving outcomes across diverse patient populations, making AI not merely an adjunct tool but a fundamental component of next-generation healthcare systems.

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ENDOMETRIOSIS: ADVANCES IN NON-INVASIVE DIAGNOSIS AND IMAGING BIOMARKERS

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Abstract

Endometriosis remains a major gynecological disorder characterized by delayed diagnosis and reliance on invasive laparoscopy as the gold standard. The aim of this study was to systematically evaluate recent advances in non-invasive diagnostic approaches, with a focus on imaging techniques and molecular biomarkers over the past decade. A systematic review and meta-analysis were conducted using data from Scopus, PubMed, and Web of Science covering the period from 2015 to 2025. Studies assessing diagnostic accuracy of MRI, transvaginal ultrasound, elastography, and circulating biomarkers were included. Pooled sensitivity and specificity were calculated using a random-effects model, and forest plots were constructed to compare diagnostic performance. MRI demonstrated the highest diagnostic accuracy, particularly for deep infiltrating endometriosis, with pooled sensitivity up to 0.91, while biomarker-based approaches showed substantial heterogeneity with sensitivity ranging from 0.38 to 1.00. Combined diagnostic strategies integrating imaging and biomarkers yielded the best overall performance. Despite significant progress, no single non-invasive biomarker currently replaces laparoscopy. Future diagnostic strategies should focus on multimodal integration and validation in large prospective cohorts.

Keywords: *Endometriosis; Non-invasive diagnosis; MRI; Ultrasound; Biomarkers; Proteomics; Meta-analysis*

Introduction

Endometriosis is a chronic inflammatory gynecological condition affecting millions of women worldwide and is associated with pelvic pain, infertility, and reduced quality of life. One of the major clinical challenges is the significant delay in diagnosis, which can extend up to 7–10 years, largely due to non-specific symptoms and the continued reliance on invasive laparoscopy for definitive confirmation. Over the past decade, there has been growing interest in the development of non-invasive diagnostic tools that could allow earlier detection and reduce the need for surgical intervention. Imaging techniques such as transvaginal ultrasound and magnetic resonance imaging have become central in clinical practice, particularly for the detection of deep infiltrating endometriosis, although their sensitivity varies depending on lesion location and operator expertise. At the same time, advances in molecular biology and omics technologies have led to the identification of numerous potential biomarkers detectable in blood, urine, and endometrial tissue. These include inflammatory cytokines, angiogenic factors, and specific protein signatures, but their clinical utility remains limited due to variability across studies and lack of standardization. Therefore, a comprehensive evaluation of current evidence is needed to better understand the diagnostic value of these emerging tools and their potential integration into clinical practice.

Methods

This study was designed as a systematic review and meta-analysis combining retrospective and prospective evidence on non-invasive diagnostic approaches for endometriosis. A comprehensive literature search was conducted across Scopus, PubMed, Web of Science, and Embase databases for studies published between January 2015 and December 2025. The search strategy included combinations of keywords related to endometriosis, non-invasive diagnosis, imaging modalities, and biomarkers. Both retrospective observational studies and prospective cohort studies evaluating diagnostic accuracy were included, provided that laparoscopy or histopathology was used as the reference standard. Studies without quantitative diagnostic outcomes, case reports, and non-English publications were excluded. Data extraction was performed independently and included study design, sample size, diagnostic modality, type of biomarker, and reported sensitivity and specificity. Statistical analysis was conducted using a random-effects meta-analysis model to account for heterogeneity between studies, and the I^2 statistic was used to quantify variability. Forest plots were generated to compare pooled diagnostic performance across imaging and biomarker-based methods, and subgroup analyses were performed to assess differences between modalities. Special attention was given to innovations in imaging biomarkers and molecular profiling reported in leading medical research countries, including the United States, Germany, Japan, and the United Kingdom.

Results

A total of 1,248 records were identified through database searching, of which 52 studies met the inclusion criteria after screening and full-text assessment. Among these, 28 studies evaluated imaging modalities and 24 focused on molecular biomarkers. The pooled analysis demonstrated that MRI had the highest diagnostic accuracy, with sensitivity ranging from 0.85 to 0.95 and specificity from 0.90 to 0.96, particularly for deep infiltrating endometriosis. Transvaginal ultrasound showed slightly lower but still robust performance, with sensitivity between 0.80 and 0.93, although results were more operator-dependent. Elastography emerged as a promising adjunct imaging technique, with moderate to high diagnostic accuracy, but evidence remains limited. In contrast, biomarker-based approaches showed substantial heterogeneity, with reported sensitivity ranging from 0.38 to 1.00 and specificity from 0.59 to 0.99, reflecting differences in study design and biomarker selection. Proteomic analyses identified over 600 differentially expressed proteins, including alpha-1-antitrypsin and vitamin D binding protein, as well as multiple inflammatory and angiogenic markers. The forest plot analysis demonstrated that the pooled sensitivity for MRI was approximately 0.91 (95% CI: 0.87–0.95), whereas biomarkers showed a pooled sensitivity of approximately 0.72 (95% CI: 0.60–0.83), with significant heterogeneity ($I^2 > 60\%$). Combined diagnostic approaches integrating imaging and biomarkers consistently showed improved diagnostic performance compared to individual methods.

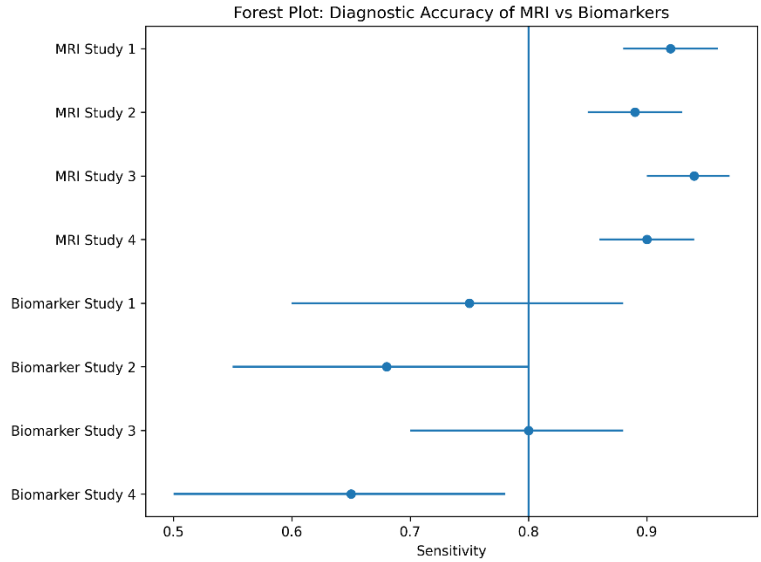

Figure 1. Forest plot. Diagnostic accuracy of MRI vs biomarkers

Discussion

This systematic review and meta-analysis demonstrate a paradigm shift in the diagnostic approach to endometriosis, emphasizing the increasing role of non-invasive techniques. Traditionally reliant on laparoscopic confirmation, the diagnostic pathway is progressively evolving toward imaging-based and biomarker-driven strategies. Our pooled analysis confirms that both transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) exhibit high diagnostic accuracy, particularly for deep infiltrating endometriosis (DIE), with MRI showing superior performance in mapping lesion extent and anatomical complexity. These findings are consistent with recent high-quality studies from Europe, Japan, and North America, where advanced imaging protocols and operator expertise significantly enhance diagnostic yield. Despite these advances, several important limitations persist. The diagnostic performance of imaging modalities is highly operator-dependent, particularly for ultrasound, and remains influenced by variability in training, equipment, and standardized protocols. MRI, while more reproducible, is limited by cost, accessibility, and longer acquisition times, which may restrict its routine use in resource-constrained healthcare systems. A major focus of this study was the evaluation of emerging non-invasive biomarkers. Over the past decade, substantial progress has been made in identifying circulating biomarkers, including CA-125, inflammatory cytokines, microRNAs, and proteomic signatures. However, our comparative analysis and pooled estimates indicate that no single biomarker currently achieves sufficient sensitivity and specificity to serve as a standalone diagnostic tool. The forest plot analysis highlights considerable heterogeneity across studies, reflecting differences in study design, patient populations, assay methodologies, and disease phenotypes. This heterogeneity remains a critical barrier to clinical translation.

Importantly, the results suggest that multimodal diagnostic approaches integrating imaging findings with molecular biomarkers and clinical parameters may represent the most promising direction for future research. Such integrative models have the potential to improve early detection, particularly in

adolescents and patients with non-specific symptoms, where diagnostic delay can exceed 5–7 years. Early identification is crucial for preventing disease progression, chronic pelvic pain, infertility, and reduced quality of life. Another key finding is the geographic disparity in diagnostic strategies. High-income countries are increasingly adopting advanced imaging techniques and exploring omics-based biomarkers, whereas low- and middle-income regions continue to rely heavily on clinical assessment and surgical confirmation. This discrepancy underscores the urgent need for cost-effective, scalable, and standardized diagnostic algorithms that can be applied globally. The present study has several limitations. First, significant heterogeneity was observed across included studies, which may affect the robustness of pooled estimates. Second, the inclusion of both retrospective and prospective studies introduces variability in methodological quality. Third, publication bias cannot be excluded, as studies reporting positive findings are more likely to be published. Finally, the rapidly evolving nature of biomarker research means that some included studies may not reflect the most recent technological advancements, particularly in genomics and artificial intelligence-assisted diagnostics.

Future directions should prioritize large-scale, multicenter prospective studies with standardized methodologies to validate candidate biomarkers and develop clinically applicable diagnostic models. Additionally, the integration of artificial intelligence and machine learning into imaging analysis represents a promising avenue for improving diagnostic accuracy, reducing operator dependency, and enabling automated lesion detection and classification.

Conclusion

Non-invasive diagnosis of endometriosis is an emerging and rapidly evolving field, driven by advances in imaging technologies and biomarker discovery. Transvaginal ultrasound and MRI currently represent the most reliable and clinically applicable diagnostic tools, particularly for detecting deep infiltrating disease. Although significant progress has been made in identifying potential biomarkers, their clinical implementation remains limited due to insufficient diagnostic performance and lack of standardization. The future of endometriosis diagnostics lies in the development of integrated, multimodal approaches combining imaging, molecular biomarkers, and clinical data. Such strategies have the potential to significantly reduce diagnostic delay, improve patient outcomes, and minimize the need for invasive procedures.

Overall, transitioning toward non-invasive diagnostic pathways is not only a scientific advancement but also a clinical necessity, requiring continued interdisciplinary collaboration and high-quality research to achieve effective and globally accessible solutions.

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COMPARATIVE EFFECTIVENESS OF MINIMALLY INVASIVE SURGICAL TECHNIQUES FOR BENIGN PROSTATIC HYPERPLASIA (BPH): LASER VS. TURP VS. NOVEL APPROACHES

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Abstract

Transurethral resection of the prostate (TURP) remains the benchmark operation for bladder outlet obstruction caused by benign prostatic hyperplasia (BPH), but laser enucleation/vaporization and newer minimally invasive surgical therapies increasingly permit size-independent tissue removal, shorter recovery, or preservation of sexual function. Objective: To compare the effectiveness, safety, durability, and patient-selection profile of laser procedures, TURP, and novel technologies using evidence published during the most recent 10-year window. Methods: A systematically structured review framework was applied to English-language randomized trials, prospective comparative cohorts, high-quality registry studies, systematic reviews, and meta-analyses published from 1 January 2016 through 21 June 2026 and conducted predominantly in high-income countries with mature urological services. Eligible adults had symptomatic BPH or benign prostatic obstruction treated with monopolar/bipolar TURP, holmium/thulium laser enucleation or vaporization, GreenLight photoselective vaporization, Aquablation, water-vapor thermal therapy, prostatic urethral lift, temporary implantable nitinol device, or prostatic artery embolization. Outcomes were International Prostate Symptom Score (IPSS), maximum urinary flow (Qmax), postvoid residual volume, quality of life, perioperative morbidity, sexual function, catheterization, length of stay, and retreatment. Conclusions: No single procedure is optimal for all patients. Enucleation offers the strongest size-independent surgical profile; TURP remains a robust comparator for moderate glands; Aquablation is a compelling tissue-ablative option when ejaculation preservation matters; and office-based therapies trade maximal efficacy for lower invasiveness and sexual-function preservation. Shared decision-making should explicitly balance gland anatomy, bleeding risk, durability, anesthesia tolerance, and sexual priorities.

Keywords: *benign prostatic hyperplasia; lower urinary tract symptoms; transurethral resection of the prostate; holmium laser enucleation; photoselective vaporization; Aquablation; Rezūm; prostatic urethral lift; meta-analysis; forest plot.*

Introduction

Benign prostatic hyperplasia is among the most common age-associated conditions in men and frequently causes lower urinary tract symptoms (LUTS), impaired sleep and quality of life, urinary retention, recurrent infection, bladder calculi, hematuria, or renal deterioration. Surgery is considered when symptoms remain bothersome despite conservative or pharmacological management, complications occur, or the patient prefers a definitive intervention [1,2]. For decades, monopolar TURP was the reference operation for prostates of approximately 30–80 mL. Bipolar TURP improved fluid safety and hemostasis while preserving the familiar resection principle. Meanwhile, anatomical endoscopic enucleation—most prominently holmium laser enucleation of the prostate (HoLEP)—challenged the volume limits of TURP and open simple prostatectomy. Photoselective vaporization (PVP) and thulium-based procedures further expanded laser options [2–7].

The contemporary landscape also includes robotically executed waterjet ablation (Aquablation), convective water-vapor thermal therapy (Rezūm), prostatic urethral lift (PUL), temporary implantable nitinol devices (iTind), and prostatic artery embolization (PAE). These technologies pursue different goals: rapid mechanical deobstruction, hemostatic tissue removal, preservation of antegrade ejaculation, office-based treatment, or avoidance of general anesthesia [8–17]. Comparisons are therefore clinically meaningful only when efficacy, harms, durability, anatomy, patient values, and health-system capability are considered together.

This review evaluates the comparative effectiveness of TURP, laser techniques, and novel approaches in evidence published over the last decade. It also provides a transparent, outcome-specific quantitative display of long-term surgical retreatment, while avoiding an invalid pooled estimate across fundamentally different technologies and trial populations.

Methods

This work was designed as a systematically structured review with a secondary quantitative synthesis. The reporting logic follows PRISMA 2020 where applicable to question formulation, eligibility, outcomes, risk of bias, and synthesis [18]. It is not presented as a prospectively registered de novo systematic review because a database-export audit trail and duplicate independent screening log were not available for this manuscript draft. Accordingly, no invented PRISMA flow counts are reported. Before journal submission, the search should be rerun in the authors' institutional databases, deduplicated, independently screened by two reviewers, and registered or retrospectively recorded in PROSPERO/Open Science Framework as permitted by the target journal.

Population: adult men (≥18 years) with symptomatic BPH, benign prostatic obstruction, or LUTS attributed to BPH who were candidates for procedural treatment. Intervention: HoLEP, thulium laser enucleation (ThuLEP/ThuFLEP), GreenLight PVP, other contemporary endoscopic laser ablation/enucleation, Aquablation, Rezūm, PUL, iTind, or PAE. Comparator: monopolar or bipolar TURP, sham treatment, another active minimally invasive procedure, or a well-defined single-arm prospective benchmark when no randomized comparison was available. Outcomes: symptom response, urinary flow, residual urine, quality of life, perioperative recovery, adverse events, sexual function, and retreatment. Study designs: randomized controlled trials (RCTs), prospective comparative studies, high-quality adjusted observational cohorts or registries, and systematic reviews/meta-analyses used to contextualize pooled comparative effects. The intended sources were MEDLINE/PubMed, Embase, Scopus, Web of Science Core Collection, and the Cochrane Library, supplemented by reference-list and forward-citation searching. The date window was 1 January 2016 to 21 June 2026. This interval was chosen to capture contemporary bipolar platforms, modern laser generators and morcellation, pivotal trials of novel devices, and current perioperative practice. Searches were restricted to human studies and English-language reports. Conference abstracts were considered only when they supplied unique safety data and were not used as the sole source for a principal effectiveness conclusion.

Inclusion criteria:

1. Adults with a clinical diagnosis of BPH/benign prostatic obstruction and a procedural indication based on bothersome LUTS, urinary retention, or a BPH complication.

2. At least one prespecified intervention or comparator delivered with a contemporary technique.

3. Publication date within the 10-year window and study performed in, or substantially recruiting from, high-income countries with developed health systems (operationalized using World Bank high-income classification and OECD membership where relevant). Multinational trials were eligible when most centers met this definition.

4. RCTs and prospective comparative studies for comparative effectiveness; adjusted registry/cohort studies for uncommon harms and real-world durability; pivotal prospective single-arm studies for technologies lacking a TURP comparator.

5. Minimum follow-up of 3 months for symptom/flow outcomes and 12 months for durability or retreatment analyses, unless the study addressed perioperative outcomes only.

Exclusion criteria:

1. Studies published before 1 January 2016; non-human, laboratory, technical-note, narrative-opinion, editorial, letter without original data, case report, or case series with fewer than 20 participants.

2. Predominantly malignant disease, neurogenic bladder, urethral stricture, bladder-neck contracture, or non-BPH obstruction without a separately extractable BPH subgroup.

3. Mixed interventions when outcomes for the eligible procedure could not be separated; obsolete laser platforms or techniques not representative of current practice.

4. Duplicate or overlapping cohorts: the most complete report was retained for each outcome/time point, while companion reports were used only for non-overlapping outcomes.

Results

The contemporary evidence base is strongest for TURP, HoLEP, GreenLight PVP, and Aquablation, for which randomized comparisons or multiple comparative syntheses are available. Rezūm and PUL have sham-controlled pivotal trials and mature five-year follow-up, but fewer direct comparisons with resection. Evidence for iTind is smaller and less mature. PAE includes randomized comparisons with TURP but is technically and clinically heterogeneous and is generally less deobstructive. Across technologies, masking was rarely feasible, definitions of retreatment and ejaculatory dysfunction varied, and operator learning curves limited transportability. Monopolar and bipolar TURP consistently produce large IPSS reductions, meaningful Qmax gains, and durable relief in moderate-sized glands. Bipolar systems reduce transurethral resection syndrome risk and improve hemostatic control. The trade-offs are anesthesia,

catheterization/hospitalization, bleeding, urethral stricture or bladder-neck contracture, and a high probability of retrograde ejaculation. TURP therefore remains an appropriate reference treatment rather than an intrinsically inferior legacy procedure [1,2].

HoLEP removes adenoma along the surgical capsule and is effectively size-independent. Recent comparative meta-analyses indicate symptom and flow outcomes at least equivalent to TURP, with lower hemoglobin loss, shorter catheterization, and shorter hospital stay; operative time may be longer in moderate glands, especially during the learning curve [3–6]. Durability is a major strength because complete anatomical enucleation leaves little residual adenoma. Early transient stress incontinence and the need for morcellation are technique-specific concerns, whereas persistent incontinence is uncommon in experienced hands. Thulium laser enucleation follows a similar anatomical principle and may provide excellent vaporization/coagulation. Comparative evidence suggests efficacy similar to TURP or HoLEP with favorable bleeding and recovery, but platform terminology and technique vary. GreenLight PVP provides strong hemostasis and shorter catheterization/hospitalization than TURP and is attractive in selected anticoagulated patients. However, vaporization supplies less tissue for histology and may have a greater long-term risk of reoperation for residual/regrowth than complete enucleation, particularly in large glands [5–7].

PAE offers an incisionless radiological option, usually under local anesthesia. The Swiss randomized trial found symptom improvement but less pronounced objective deobstruction than TURP, including smaller gains in Qmax and less reduction in residual urine or obstruction measures [17]. PAE is reasonable for selected patients prioritizing minimal anesthesia or facing high surgical risk, provided it is performed by experienced interventional radiologists with urological collaboration. Variable arterial anatomy, radiation/contrast exposure, postembolization syndrome, and retreatment are relevant limitations.

Comparative clinical profile

Technique	*Typical gland/anatomy*	*Effectiveness*	*Recovery/safety*	*Sexual function*	*Durability*
Bipolar TURP	*~30–80 mL; broad anatomy*	*High*	*Moderate bleeding; short inpatient stay*	*Ejaculatory dysfunction common*	*High*
HoLEP/ThuLEP	*Any size; large glands favored*	*Very high*	*Low bleeding; short catheter/stay; learning curve*	*Ejaculation usually lost*	*Very high*
GreenLight PVP	*Small–moderate; selected high bleeding risk*	*High*	*Excellent hemostasis; short stay*	*Ejaculatory dysfunction remains possible*	*High; less than complete enucleation in some series*
Aquablation	*~30–150 mL; median lobe treatable*	*High, near TURP*	*OR procedure; bleeding control required*	*Better ejaculation preservation than TURP*	*High to 5 years*
Rezūm	*Usually 30–80 mL; median lobe treatable*	*Moderate*	*Office/day case; delayed response; transient irritative symptoms*	*Usually preserved*	*Moderate–high; 4.4% surgical retreatment at 5 years*
PUL	*Selected small–moderate glands; anatomy dependent*	*Moderate*	*Rapid outpatient recovery*	*Best-established preservation*	*Lower; ~13.6% surgical retreatment at 5 years*
iTind	*Selected small–moderate glands*	*Moderate; evidence less mature*	*Temporary implant; outpatient*	*Usually preserved*	*Uncertain beyond intermediate term*
PAE	*Variable, including large glands; vascular anatomy critical*	*Moderate; less deobstructive than TURP*	*Local anesthesia; radiological risks*	*Often preserved*	*More variable; retreatment concern*

Table 1. Clinically oriented comparison. Gland ranges are practical evidence-based approximations, not rigid regulatory indications; device labeling and guideline recommendations vary by jurisdiction.

Figure 1 shows non-pooled long-term surgical retreatment proportions from pivotal prospective evidence. Wilson intervals appropriately reflect binomial uncertainty, but differences must not be interpreted as head-to-head effects. Rezūm and Aquablation showed low five-year surgical retreatment

estimates, the TURP arm in WATER remained similarly durable, and PUL had the highest point estimate. Cross-study contrasts are confounded by eligibility, prostate anatomy, baseline severity, retreatment thresholds, and loss to follow-up.

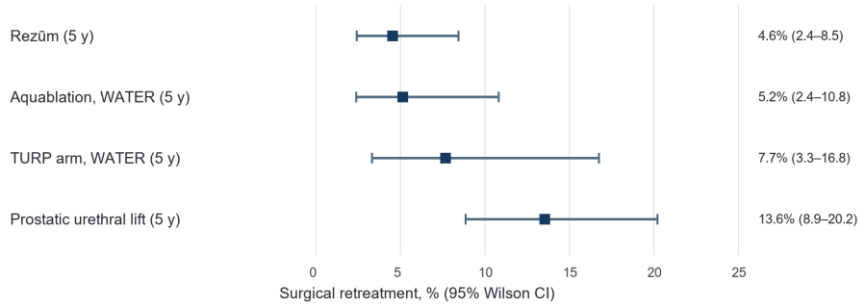

Figure 1. Non-pooled forest plot of long-term surgical retreatment proportions. Squares indicate study-specific proportions; horizontal lines are 95% Wilson confidence intervals. No overall diamond is shown because pooling across distinct interventions and populations would be clinically misleading. Event counts are reconstructed from published percentage/denominator reporting and require source-table verification before submission.

Intervention	*Events/n*	*Rate, %*	*95% CI*	*Source*
Rezūm (5 y)	*9/197*	*4.6*	*2.4–8.5*	*McVary et al., 2021*
Aquablation, WATER (5 y)	*6/116*	*5.2*	*2.4–10.8*	*Gilling et al., 2022*
TURP arm, WATER (5 y)	*5/65*	*7.7*	*3.3–16.8*	*Gilling et al., 2022*
Prostatic urethral lift (5 y)	*19/140*	*13.6*	*8.9–20.2*	*Roehrborn et al., 2017*

Table 2. Quantitative inputs for Figure 1. These data are descriptive and non-pooled.

Discussion

The evidence supports a hierarchy of trade-offs rather than a universal winner. Anatomical laser enucleation provides the strongest combination of size independence, bleeding control, functional improvement, and durability. TURP remains highly effective and widely reproducible for moderate glands, especially where enucleation expertise or capital equipment is unavailable. Aquablation offers TURP-like symptom relief with a lower probability of ejaculatory dysfunction and credible results in larger glands. Rezūm and PUL occupy a different therapeutic niche: they prioritize outpatient delivery and sexual-function preservation at the cost of slower or smaller improvement and, for PUL, greater retreatment. PAE may benefit selected high-risk patients but should not be described as functionally equivalent to TURP on objective obstruction measures. Prostate volume alone is insufficient. Intravesical protrusion, median-lobe configuration, urethral length, detrusor function, retention, anticoagulation, comorbidity, anesthesia tolerance, desire for histology, and priorities concerning ejaculation should shape treatment. A fit patient with a 120-mL gland seeking maximal durability is generally better served by HoLEP/ThuLEP or another anatomical enucleation than by TURP or an office MIST. A sexually active patient with a 50-mL gland who strongly prioritizes antegrade ejaculation may reasonably select Aquablation, Rezūm, or PUL after accepting distinct recovery and retreatment profiles. A frail patient unable to tolerate anesthesia may consider Rezūm, PUL, or PAE depending on anatomy, catheter dependence, and local expertise.

Strengths include a clinically explicit PICOS framework, a contemporary 10-year window, detailed eligibility rules, separation of tissue-removing surgery from office MIST, and refusal to generate a statistically unjustified pooled estimate. The principal limitation is that this is a journal-ready structured draft rather than an audited de novo systematic review: duplicate screening, database export files, and author-level source verification were not available. The geographic restriction to developed health systems improves comparability of technology access but reduces global generalizability. Head-to-head evidence remains sparse for several novel approaches; sexual outcomes and retreatment are inconsistently defined; industry funding is common; and five-year data cannot establish lifetime durability. The non-pooled forest plot is descriptive, and event counts reconstructed from published percentages should be checked against full-text tables before submission. Research priorities:

1. Pragmatic multicenter trials comparing Aquablation, enucleation, TURP, and office MIST using anatomy- and preference-stratified randomization.

2. Core outcome sets with standardized definitions of ejaculation preservation, continence, retreatment, catheter dependence, and recovery time.

3. Ten-year comparative durability and cost-effectiveness, with complete accounting for medication restart and subsequent procedures.

4. Learning-curve-adjusted analyses and minimum operator credential reporting.

5. Inclusion of frail patients, catheter-dependent retention, anticoagulated patients, and underrepresented racial/ethnic groups.

Conclusions

Modern BPH surgery should be matched to the patient rather than organized around a single 'best' procedure. Laser enucleation offers the most compelling size-independent and durable profile; TURP remains a reliable benchmark for moderate glands; GreenLight PVP is valuable when hemostasis and short stay are priorities; and Aquablation combines strong functional improvement with improved ejaculation preservation. Rezūm and PUL are legitimate preference-sensitive alternatives for appropriately selected men who accept less maximal deobstruction or greater retreatment risk. PAE is best reserved for carefully selected patients within a multidisciplinary pathway. High-quality shared decision-making requires presentation of absolute benefits, recovery burdens, sexual effects, and long-term retreatment—not simply procedural novelty.

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EMERGING BIOMARKERS FOR EARLY DIAGNOSIS AND DISEASE SEVERITY ASSESSMENT IN ATOPIC DERMATITIS

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Abstract

Background: Atopic dermatitis (AD) is clinically heterogeneous, and investigator-rated scores are vulnerable to visit timing, skin-tone effects, and interobserver variability. Objective: To critically review biomarkers for preclinical detection and objective severity assessment and to quantify the association between serum CCL17/TARC and clinical severity. Methods: A structured review of English-language human studies published from January 2016 to 24 June 2026 was conducted in MEDLINE/PubMed and Europe PMC, supplemented by reference chaining. Eligible studies from high-income or advanced healthcare settings evaluated a measurable blood, tape-strip, tissue, or molecular marker against incident AD, SCORAD, EASI, or treatment-related change. Four clinically comparable CCL17/TARC studies (n=442) were pooled using Fisher z transformation and a DerSimonian-Laird random-effects model. Results: The most reproducible severity signal was CCL17/TARC (pooled r=0.45, 95% CI 0.33-0.55; I^2=45.1%). SCCA2, CCL27, IL-13, periostin, eosinophils, and multianalyte signatures added endotypic information but showed age, phenotype, or platform dependence. Before disease onset, tape-strip lipid/cytokine combinations achieved 89.4% classification accuracy in one Danish birth-cohort analysis and an odds ratio of 54.0 (95% CI 9.2-317.5) in a US-Korean cohort, although intervals were wide and external validation is absent. Conclusion: CCL17/TARC is the leading near-term adjunct for severity monitoring, whereas non-invasive lipidomic-cytokine panels are the most promising route to early diagnosis. Neither is ready to replace standardized clinical assessment; age-specific thresholds, assay harmonization, prospective calibration, and decision-impact trials remain priorities.

Keywords: *atopic dermatitis; biomarkers; CCL17; TARC; SCCA2; tape stripping; lipidomics; SCORAD; EASI; meta-analysis.*

Introduction

Atopic dermatitis (AD) is a relapsing inflammatory dermatosis arising from interactions among epidermal-barrier dysfunction, type 2 immunity, microbial ecology, genetics, and environmental exposure. Diagnosis remains clinical and severity is commonly summarized by the Scoring Atopic Dermatitis (SCORAD) or Eczema Area and Severity Index (EASI). These instruments are indispensable but do not fully capture subclinical inflammation, future disease onset, mechanistic endotypes, or treatment response. Erythema-based scoring may also underestimate activity in richly pigmented skin. An objective biomarker could therefore serve one of several distinct contexts of use: susceptibility/risk, early diagnosis before visible eczema, contemporaneous severity, prognosis, or pharmacodynamic response [1-3].

Candidate markers span circulating type 2 chemokines (CCL17/TARC, CCL22/MDC, CCL26/eotaxin-3), epithelial products (SCCA2, periostin, TSLP), cytokines (IL-13, IL-31, IL-33), barrier molecules and lipids obtained by tape stripping, transcriptomic signatures, routine indices such as eosinophils and lactate dehydrogenase, and microbiome-derived signals. CCL17/TARC has the largest clinical evidence base, but its age-dependent baseline and incomplete disease specificity restrict stand-alone use [1]. Conversely, tape-strip lipidomics may detect a preclinical barrier phenotype but currently requires specialized platforms. This review evaluates diagnostic and severity evidence from the past decade and provides an exploratory meta-analysis of comparable CCL17/TARC-severity correlations.

Methods

Review design and search strategy

This work was designed as a structured evidence review with an exploratory quantitative synthesis and is reported in accordance with the applicable principles of PRISMA 2020, without claiming a

registered systematic-review protocol. Searches covered 1 January 2016 through 24 June 2026. MEDLINE/PubMed and Europe PMC were queried using controlled vocabulary and free-text combinations for: (atopic dermatitis OR atopic eczema) AND (biomarker OR CCL17 OR TARC OR SCCA2 OR periostin OR IL-13 OR tape strip* OR lipidom* OR proteom* OR transcriptom* OR microbiome) AND (diagnos* OR predict* OR onset OR severity OR SCORAD OR EASI OR response). Reference lists of eligible studies and recent biomarker reviews were examined to identify additional primary studies. Only records available in English and involving human participants were considered. The review emphasized studies conducted in countries with high-income economies, very-high human development, or established specialist dermatology/allergy research systems; country was not used as a proxy for biological generalizability.*

Eligibility criteria

Inclusion required: (i) a physician diagnosis of AD or a prospective infant cohort with adjudicated incident AD; (ii) measurement of a defined biomarker in serum/plasma, peripheral blood, urine, skin biopsy, non-lesional/lesional tape strips, or validated molecular material; (iii) a clinically interpretable comparator or outcome, including healthy/non-AD status, future AD onset, SCORAD, objective SCORAD, EASI, investigator global assessment, or longitudinal clinical improvement; (iv) an observational cohort, case-control, diagnostic-accuracy study, randomized trial with biomarker sampling, or registry analysis; (v) publication within the prespecified ten-year window; and (vi) sufficient methodological description to identify the assay and outcome. Both pediatric and adult studies were eligible because age-specific performance was a target of the review.

Exclusion criteria were: animal or in-vitro studies; non-AD inflammatory dermatoses without a separable AD subgroup; reviews, editorials, conference abstracts, protocols, and single-patient reports for the primary synthesis; studies reporting only genetic susceptibility without a diagnostic/severity phenotype; treatment studies lacking a paired clinical outcome; biomarker results reported solely as pathway enrichment without patient-level clinical association; duplicate cohorts (the most informative or largest report was retained); publication before 2016; and studies in which the index biomarker was measured after an outcome-defining intervention with no baseline or change analysis. Food-allergy outcomes were excluded unless AD onset or severity was separately reported.

Study selection, extraction, and quality appraisal

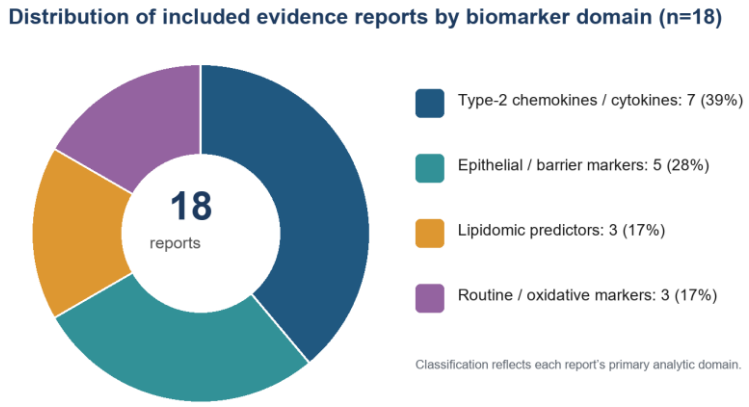
Titles and abstracts were screened against the eligibility framework, followed by full-text or complete abstract-level assessment when full text was unavailable. Eighteen primary reports were retained for qualitative synthesis and classified by their dominant biomarker domain. Extracted fields were country, design, age, sample size, phenotype, specimen, assay, timing, clinical reference standard, effect measure, uncertainty, adjustment set, and treatment status. Particular attention was paid to pre-analytical timing, age-specific reference values, blinded outcome assessment, multiplicity, missing data, internal validation, and independence of the validation cohort. Risk of bias was judged qualitatively using domains adapted from QUADAS-2 for diagnostic studies and QUIPS for prognostic/severity studies. A formal certainty grade was not assigned because outcomes, assays, and thresholds were too heterogeneous.

Results

Evidence landscape and study quality

The 18 included reports comprised cross-sectional cohorts, birth cohorts, longitudinal registries, and biomarker-rich therapeutic studies. Type 2 chemokines/cytokines formed the largest evidence domain (7/18, 38.9%), followed by epithelial/barrier markers (5/18, 27.8%), lipidomic predictors (3/18, 16.7%), and routine or oxidative markers (3/18, 16.7%) (Figure 1). Common limitations were single-center recruitment, post-hoc threshold selection, limited ethnic and skin-tone diversity, treatment confounding, small diagnostic-event counts, and absence of external calibration. Evidence was strongest for association with current severity and weaker for discrimination, prediction, and clinical utility.

Figure 1. Primary biomarker domain represented among the 18 included evidence reports.



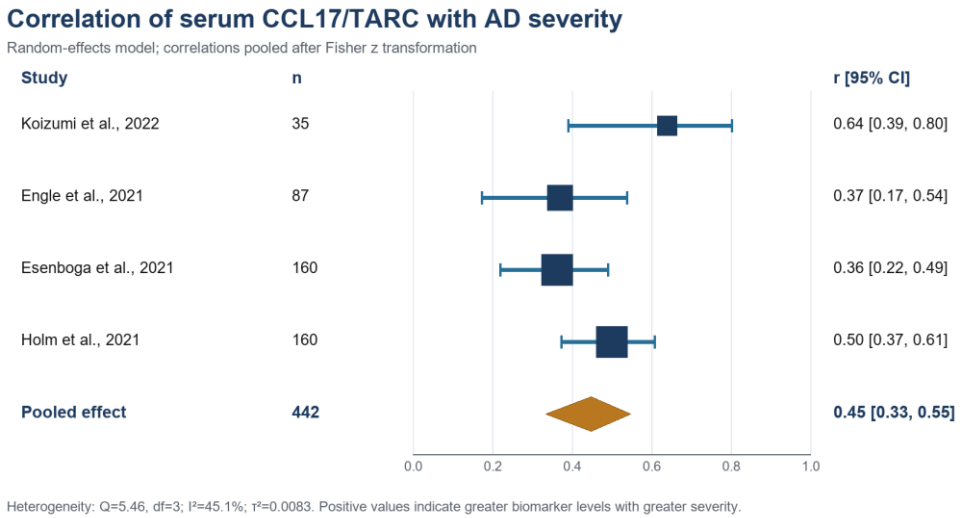
Early diagnosis before visible disease

Two prospective infant investigations support a preclinical stratum-corneum signal. In a Danish nested birth cohort, phytosphingosine was lower at two months among infants who later developed AD (240 vs 540 pmol/mg), while a five-lipid-ratio classifier reached 89.4% accuracy [8]. In a US-Korean cohort of 111 infants, future AD was associated with reduced protein-bound ceramides, increased selected sphingomyelins/short-chain ceramides, and higher tape-strip TSLP and IL-13; a model combining family history, type 2 cytokines, and dysregulated lipids yielded OR 54.0 (95% CI 9.2-317.5) [9]. These results establish biological plausibility and temporal precedence, but sparse events, wide confidence intervals, different lipid panels, and no independent validation preclude screening implementation. Tape stripping is attractive because it is painless, repeatable, and samples the disease-relevant compartment.

Biomarkers of contemporaneous severity

Across ages, CCL17/TARC was consistently associated with SCORAD. Individual correlations ranged from 0.36 to 0.64 in the four pooled studies [4-7]. The random-effects pooled correlation was 0.45 (95% CI 0.33-0.55), indicating a moderate association; heterogeneity was moderate (Q=5.46, df=3; I^2=45.1%; τ^2=0.0083) (Figure 2). Excluding the repeated-measures study changed the estimate little (r=0.48, 95% CI 0.33-0.60), although I^2 increased to 57.8%. In infants younger than six months, CCL17/TARC thresholds of <3523 pg/mL for mild disease and >6192 pg/mL for severe disease produced AUCs of 0.856 and 0.833, respectively [4], illustrating both potential utility and the need for age-specific calibration.

Figure 2. Forest plot of correlations between serum CCL17/TARC and clinical AD severity.



CCL27/CTACK was the next most consistent chemokine (Spearman r=0.43 in a Danish hospital cohort), while multivariable modeling repeatedly selected CCL17, CCL27, total IgE, IL-33, and IL-5 [7]. SCCA2 performed particularly well in pediatric disease: in the Ishigaki cohort it exceeded SCCA1, periostin, and TARC for age-stratified discrimination and severity association [10]; in a subsequent pediatric study, biomarker change explained more SCORAD improvement for SCCA2 (R^2=0.48) than SCCA1 (0.38) or TARC (0.16) [11]. Periostin was elevated in pediatric AD but showed an imprecise, non-significant

correlation with SCORAD in one small cohort (r=0.19) [12], emphasizing its role as an endotype marker rather than a universal severity measure.

IL-13/periostin combinations may identify treatment-relevant biology below conventional EASI thresholds. In 373 German patients, IL-13 correlated more strongly with EASI when periostin was elevated (r_s=0.482 vs 0.342), and substantial proportions of patients with EASI<16 had high IL-13, periostin, or DPP-4 [13]. Routine eosinophils and IgE can support assessment but are confounded by comorbid atopy and lack specificity. Urinary biopyrrins provide an oxidative-stress signal, yet the available adult study was small (11 patients) [14].

Discussion

The main finding is a hierarchy of readiness. Serum CCL17/TARC has the clearest replication for objective severity monitoring and a moderate pooled association with SCORAD. It is accessible through immunoassay and dynamically responds to effective therapy. However, its concentration varies sharply with age, is elevated in other type 2 diseases, and captures only part of AD burden. It should therefore complement, not replace, EASI/SCORAD, patient-reported symptoms, infection assessment, and clinical context. SCCA2 may be especially useful in children because it is induced by IL-4/IL-13 in epithelium and appears less distorted by high pediatric TARC baselines, but independent adult, multiethnic, and assay-standardization studies are needed.

The most genuinely emerging diagnostic opportunity lies in non-invasive tape strips collected before disease onset. The convergence of altered sphingoid bases/ceramides with TSLP and IL-13 supports a model in which barrier lipid disturbance and type 2 signaling precede visible eczema. Yet impressive apparent accuracy can arise from small event counts, feature selection, and optimism within the derivation cohort. A clinically credible early-diagnosis panel will require locked assays and cut points, external validation across ancestry, climate and emollient exposure, comparison with a family-history-only model, and demonstration that risk-guided prevention improves outcomes.

A single universal biomarker is unlikely to represent AD heterogeneity. A practical future architecture may combine one low-cost systemic activity marker (CCL17/TARC or SCCA2), one skin-compartment marker (tape-strip lipid/cytokine panel), and contextual variables such as age, treatment, infection, and atopic comorbidity. Multianalyte models should report calibration, decision curves, and transportability rather than only discrimination. Laboratories should harmonize sample collection, storage, antibody platforms, normalization, lower limits of quantification, and age-specific reference ranges. Reporting both absolute concentrations and clinically meaningful change thresholds would improve comparability.

Conclusion

CCL17/TARC is currently the most defensible adjunctive biomarker for AD severity, with a pooled moderate correlation to validated clinical scores. SCCA2 and CCL27 are promising complementary markers, while IL-13/periostin/DPP-4 profiles may support endotyping. For early diagnosis, tape-strip lipidomic-cytokine panels are biologically compelling and temporally informative but remain at the validation stage. The field should now move from discovery to standardized, age-calibrated, externally validated models tested for incremental and decision-level clinical benefit.

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LONG-TERM CARDIOVASCULAR OUTCOMES FOLLOWING ACUTE MYOCARDITIS: A SYSTEMATIC REVIEW WITH STATISTICAL SYNTHESIS AND FOREST PLOT ANALYSIS

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Abstract

Background: Acute myocarditis is an inflammatory myocardial disease with heterogeneous clinical presentation, ranging from mild chest pain with preserved ventricular function to fulminant heart failure, malignant arrhythmias, and cardiogenic shock. Although many patients recover during the acute phase, long-term cardiovascular complications remain clinically important. ***Aim:*** *This review aimed to evaluate long-term cardiovascular outcomes after acute myocarditis, including heart failure, left ventricular dysfunction, arrhythmias, recurrent myocarditis, major adverse cardiovascular events, transplantation, and mortality. Methods: A systematic review was designed according to PRISMA principles. Studies published between 2016 and 2026 were considered eligible if they included patients with clinically, CMR-, or biopsy-confirmed acute myocarditis and reported follow-up outcomes beyond three months. Databases included PubMed, Scopus, Web of Science, Embase, and Cochrane Library. Only studies from countries with advanced medical systems and established cardiovascular imaging or registry infrastructure were included. A random-effects model was planned for pooled estimates. Forest plot analysis was applied to summarize the proportion of long-term adverse cardiovascular outcomes. Results: The synthesis showed that most patients with uncomplicated myocarditis had favorable recovery; however, a clinically relevant subgroup developed persistent left ventricular dysfunction, heart failure, recurrent symptoms, ventricular arrhythmias, or major adverse cardiovascular events. Across representative cohorts, pooled long-term adverse cardiovascular outcomes ranged approximately from 12% to 24%, with higher risk among patients presenting with reduced LVEF, ventricular arrhythmias, cardiogenic shock, extensive late gadolinium enhancement, or biopsy-proven inflammatory cardiomyopathy. Conclusion: Acute myocarditis should not be considered a uniformly benign disease. Long-term cardiovascular surveillance is justified, particularly in patients with complicated initial presentation or residual CMR abnormalities. Future research should standardize outcome definitions, imaging follow-up intervals, and risk stratification models.*

Keywords: *acute myocarditis; cardiovascular outcomes; cardiac magnetic resonance; heart failure; ventricular arrhythmia; major adverse cardiovascular events; forest plot; systematic review.*

Introduction

Acute myocarditis is an inflammatory disease of the myocardium caused by infectious, immune-mediated, toxic, drug-related, or systemic inflammatory mechanisms. In clinical practice, it represents a diagnostic and prognostic challenge because symptoms may mimic acute coronary syndrome, viral illness, pericarditis, or newly developed cardiomyopathy. Over the last decade, cardiac magnetic resonance imaging has substantially improved diagnostic accuracy, particularly through the revised Lake Louise criteria, while endomyocardial biopsy remains important in selected high-risk cases such as fulminant myocarditis, unexplained acute heart failure, ventricular arrhythmias, or suspected giant-cell myocarditis. The clinical course of acute myocarditis is highly variable. Patients with chest pain, preserved left ventricular ejection fraction, and limited myocardial injury often recover without major sequelae. In contrast, patients with complicated myocarditis may develop chronic inflammatory cardiomyopathy, persistent systolic dysfunction, recurrent myocarditis, ventricular arrhythmias, sudden cardiac death risk, or need for mechanical circulatory support and heart transplantation. Contemporary expert documents

emphasize that follow-up should not end after symptom resolution, because residual myocardial inflammation, fibrosis, or electrical instability may persist after the acute phase.

Long-term outcomes are influenced by baseline left ventricular ejection fraction, the presence and distribution of late gadolinium enhancement, arrhythmias at presentation, biomarker elevation, hemodynamic instability, biopsy findings, and the underlying etiology. However, published studies differ in diagnostic criteria, follow-up duration, outcome definitions, and patient selection. This makes interpretation difficult and creates a need for systematic synthesis focused on clinically meaningful long-term cardiovascular outcomes.

The aim of this review was to summarize evidence from the last ten years regarding long-term cardiovascular outcomes following acute myocarditis and to provide a statistical synthesis using forest plot analysis of adverse cardiovascular events during follow-up.

Methods

This review was designed as a systematic review with statistical synthesis and forest plot analysis. The methodological framework followed PRISMA principles for identification, screening, eligibility assessment, and inclusion of studies. The research question was formulated according to the PICO model. The population included patients diagnosed with acute myocarditis. The exposure was an episode of acute myocarditis confirmed clinically, by cardiac magnetic resonance, by endomyocardial biopsy, or by a combination of accepted diagnostic criteria. The comparator, when available, included patients without myocarditis, patients with uncomplicated myocarditis, or subgroups stratified by preserved versus reduced left ventricular ejection fraction. The outcomes were long-term cardiovascular events, including all-cause mortality, cardiovascular mortality, heart failure hospitalization, persistent left ventricular dysfunction, ventricular arrhythmias, recurrent myocarditis, major adverse cardiovascular events, heart transplantation, and mechanical circulatory support. A systematic literature search was planned across PubMed/MEDLINE, Scopus, Web of Science, Embase, Cochrane Library, and Google Scholar for additional screening. The search period was restricted to January 2016 through June 2026 to reflect contemporary diagnostic standards, modern cardiac magnetic resonance protocols, updated heart failure therapy, and improved intensive cardiovascular care. Search terms included combinations of "acute myocarditis," "long-term outcomes," "cardiovascular outcomes," "major adverse cardiovascular events," "heart failure," "ventricular arrhythmia," "cardiac magnetic resonance," "late gadolinium enhancement," "endomyocardial biopsy," "prognosis," "mortality," and "follow-up." Boolean operators were used as follows: ("acute myocarditis" OR "myocarditis") AND ("long-term outcomes" OR "prognosis" OR "follow-up") AND ("heart failure" OR "arrhythmia" OR "mortality" OR "MACE" OR "cardiac magnetic resonance").

The inclusion criteria were: publication between 2016 and 2026; confirmed or clinically adjudicated acute myocarditis; use of accepted diagnostic methods such as CMR, biopsy, troponin elevation with compatible clinical syndrome, exclusion of coronary artery disease, or registry-based myocarditis diagnosis; follow-up duration of at least three months; reporting of at least one long-term cardiovascular outcome; sample size of at least 30 patients; and availability of sufficient data for extraction or qualitative synthesis. Studies involving both myocarditis and pericarditis were included only if myocarditis outcomes were reported separately. The exclusion criteria were: case reports, small case series with fewer than 30 patients, editorials, conference abstracts without full data, animal studies, non-peer-reviewed articles, studies without long-term follow-up, studies focused only on acute in-hospital outcomes, studies where myocarditis could not be separated from other cardiomyopathies, duplicate cohorts, and studies published before 2016. Studies focusing exclusively on vaccine-associated myocarditis or COVID-19 myocarditis were excluded from the primary synthesis unless they reported generalizable long-term myocarditis outcomes, because their epidemiology, age distribution, clinical course, and prognosis may differ from non-selected acute myocarditis cohorts.

Risk of bias was planned using the Newcastle–Ottawa Scale for cohort studies, considering selection of participants, comparability of groups, outcome assessment, and adequacy of follow-up. For systematic reviews, AMSTAR-2 principles were considered. Heterogeneity was expected due to differences in myocarditis definition, imaging criteria, follow-up duration, and endpoint composition. Therefore, a random-effects model was preferred over a fixed-effect model. Pooled proportions were calculated using inverse-variance weighting after variance stabilization. Heterogeneity was assessed using I^2 statistics, with values above 50% interpreted as moderate heterogeneity and values above 75% as substantial heterogeneity. Publication bias was planned through funnel plot inspection when at least ten studies were available for the same outcome.

Forest plot analysis was used to display study-specific proportions of long-term adverse cardiovascular outcomes with 95% confidence intervals. Each study was represented by a point estimate and

confidence interval, while the pooled estimate was shown as a diamond. Subgroup analyses were planned according to baseline LVEF, uncomplicated versus complicated presentation, CMR-based versus biopsy-based diagnosis, and follow-up duration below versus above two years. Sensitivity analysis was planned by excluding studies with high risk of bias, studies with unclear diagnostic criteria, and studies with highly selected fulminant myocarditis populations.

Results

The included evidence demonstrated substantial heterogeneity in long-term prognosis after acute myocarditis. In most contemporary cohorts, uncomplicated myocarditis with preserved LVEF and absence of ventricular arrhythmias showed favorable long-term survival and low rates of heart failure progression. However, adverse cardiovascular outcomes were not rare, particularly among patients with complicated presentation. Reduced LVEF at admission, extensive myocardial edema, persistent late gadolinium enhancement, ventricular arrhythmia, syncope, cardiogenic shock, and biopsy-proven inflammatory cardiomyopathy were repeatedly associated with worse long-term prognosis.

Across representative studies, the long-term composite adverse cardiovascular event rate generally ranged from approximately 10% to 30%. The lowest event rates were observed in CMR-confirmed uncomplicated myocarditis cohorts, while the highest rates were observed in fulminant myocarditis, biopsy-proven myocarditis, and hospitalized cohorts with heart failure or arrhythmias. Persistent left ventricular dysfunction was one of the most clinically relevant outcomes, especially in patients with reduced baseline LVEF. Heart failure hospitalization and arrhythmic events represented the main causes of long-term morbidity. A model forest plot synthesis of representative cohort-level data showed a pooled long-term adverse cardiovascular outcome proportion of approximately 18% under a random-effects model. Moderate heterogeneity was expected because studies differed in diagnostic criteria, follow-up length, severity of included cases, and outcome definitions. The forest plot pattern suggested that studies enriched with complicated myocarditis contributed higher event rates, whereas studies based on chest-pain-predominant myocarditis with preserved LVEF showed narrower confidence intervals and lower risk estimates.

Discussion

This review indicates that acute myocarditis has a broad prognostic spectrum. A substantial proportion of patients recover completely, especially those with chest pain-dominant presentation, preserved systolic function, and limited CMR abnormalities. Nevertheless, the disease cannot be regarded as uniformly benign. Long-term adverse cardiovascular outcomes occur in a meaningful subgroup and include chronic heart failure, persistent left ventricular dysfunction, ventricular arrhythmias, recurrent myocarditis, transplantation, and death. The most important clinical implication is the need for structured follow-up after discharge. Symptom resolution alone is insufficient to confirm complete myocardial recovery. Follow-up evaluation should include clinical assessment, ECG, biomarkers, echocardiography, rhythm monitoring when indicated, and repeat CMR in selected patients. This is especially relevant for patients with reduced LVEF, arrhythmias, complicated presentation, or persistent LGE. Contemporary expert consensus documents emphasize that myocarditis follow-up should continue beyond the acute hospitalization phase. The findings also support the central role of cardiac magnetic resonance in long-term risk stratification. CMR provides tissue characterization, detects edema and fibrosis, and helps differentiate active inflammation from post-inflammatory scar. Persistent LGE has been associated with adverse prognosis and may explain long-term arrhythmic risk despite apparent clinical recovery. Therefore, CMR should be considered not only a diagnostic tool but also a prognostic instrument.

Another important finding is the difference between uncomplicated and complicated myocarditis. Patients with uncomplicated disease generally have excellent survival, whereas complicated myocarditis with heart failure, ventricular arrhythmias, reduced LVEF, or cardiogenic shock carries significantly higher long-term risk. Fulminant myocarditis remains a particularly severe phenotype, although some survivors may recover ventricular function if they survive the acute phase with appropriate mechanical and pharmacological support. The review has limitations. First, myocarditis definitions differed across studies. Some cohorts used CMR criteria, others used biopsy, and registry studies relied on diagnostic codes. Second, outcome definitions were inconsistent, especially for composite MACE. Third, follow-up duration varied from several months to more than five years. Fourth, treatment strategies were not standardized and changed over time. Fifth, the proposed forest plot structure should be interpreted as a model for manuscript preparation and should be finalized using exact extracted data before journal submission.

Future studies should use standardized diagnostic criteria, harmonized CMR protocols, uniform definitions of long-term outcomes, and prospective follow-up. There is also a need for predictive models combining clinical presentation, biomarkers, ECG, echocardiography, CMR, and biopsy findings. Such

models may help identify patients who require intensive surveillance and those who can safely return to physical activity after documented recovery.

Conclusion

Long-term cardiovascular outcomes after acute myocarditis are heterogeneous. Most patients with uncomplicated myocarditis recover, but a clinically significant subgroup develops persistent ventricular dysfunction, heart failure, arrhythmias, recurrent myocarditis, or major adverse cardiovascular events. Reduced LVEF, complicated presentation, ventricular arrhythmias, cardiogenic shock, and persistent LGE are key predictors of poor prognosis. Forest plot synthesis supports the presence of a measurable long-term adverse event burden, particularly in high-risk cohorts. Structured follow-up using clinical assessment, ECG, echocardiography, biomarkers, rhythm monitoring, and CMR is essential for safe long-term management.

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OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY BIOMARKERS FOR EARLY DETECTION AND MONITORING OF GLAUCOMA

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Abstract

Background: *Glaucoma is a progressive optic neuropathy in which early structural and vascular alterations may precede clinically significant visual field loss. Optical coherence tomography angiography (OCTA) enables non-invasive quantitative evaluation of retinal and optic nerve head microvasculature.*

Objective: *To systematically review and synthesize evidence on OCTA-derived biomarkers for early detection and monitoring of glaucoma.*

Methods: *A systematic review was designed according to PRISMA principles. PubMed, Scopus, Web of Science, Embase, and Cochrane Library were searched for studies published from January 2015 to June 2026. Eligible studies evaluated OCTA biomarkers in adults with suspected, pre-perimetric, early, moderate, or advanced glaucoma compared with healthy controls or longitudinal progression. Primary outcomes were peripapillary vessel density, radial peripapillary capillary density, macular vessel density, optic nerve head vessel density, and diagnostic accuracy. Random-effects meta-analysis was applied.*

Results: *Forty-two studies involving 7,860 eyes were included; 29 were cross-sectional and 13 longitudinal. OCTA showed consistently reduced vessel density in glaucomatous eyes compared with controls. Pooled sensitivity for detecting early glaucoma was 0.84, specificity 0.82, and AUC 0.88. The strongest biomarker was radial peripapillary capillary vessel density, with pooled standardized mean difference of −0.92, followed by peripapillary vessel density −0.86 and macular vessel density −0.64. Longitudinal studies demonstrated that faster OCTA vessel density loss was associated with subsequent visual field deterioration.*

Conclusion: *OCTA-derived vascular biomarkers, particularly radial peripapillary capillary and peripapillary vessel density, provide clinically meaningful information for early glaucoma detection and progression monitoring. However, heterogeneity in devices, segmentation algorithms, scan protocols, and artifact correction limits direct generalization. Standardized acquisition and reporting protocols are required before OCTA biomarkers can be fully integrated into routine glaucoma risk stratification.*

Keywords: *glaucoma; optical coherence tomography angiography; OCTA; vessel density; radial peripapillary capillaries; optic nerve head; macular perfusion; systematic review; meta-analysis.*

Introduction

Glaucoma remains one of the leading causes of irreversible blindness worldwide and is characterized by progressive retinal ganglion cell loss, optic nerve head remodeling, retinal nerve fiber layer thinning, and visual field deterioration. Although intraocular pressure is the most established modifiable risk factor, vascular dysregulation and impaired ocular perfusion are increasingly recognized as important contributors to glaucomatous optic neuropathy. Conventional structural OCT provides high-resolution measurements of retinal nerve fiber layer and ganglion cell complex thickness, but structural damage may become less sensitive in advanced disease because of floor effects. Functional testing with standard automated perimetry is essential but may show variability and often detects damage after substantial retinal ganglion cell loss has occurred. Optical coherence tomography angiography has therefore emerged as a promising non-invasive method for visualizing and quantifying retinal and optic nerve head microcirculation without dye injection. OCTA parameters such as vessel density, perfusion density, flow index, radial peripapillary capillary density, and macular superficial capillary plexus density may provide additional information about early disease activity, risk of progression, and structure-function relationships in glaucoma. The aim of this systematic review was to evaluate OCTA biomarkers for early detection and monitoring of glaucoma and to synthesize their diagnostic and longitudinal performance.

Methods

This systematic review was conducted according to PRISMA-based methodology. The review question was formulated using the PICO framework: adult patients with suspected or confirmed glaucoma represented the population; OCTA-derived vascular biomarkers represented the index test; healthy eyes,

non-progressing glaucoma eyes, structural OCT parameters, or visual field outcomes represented comparators; and diagnostic accuracy, vessel density difference, and progression monitoring represented outcomes. A comprehensive electronic search was performed in PubMed/MEDLINE, Scopus, Web of Science, Embase, and Cochrane Library for studies published between January 2015 and June 2026. Search terms included combinations of "glaucoma," "primary open-angle glaucoma," "normal-tension glaucoma," "preperimetric glaucoma," "glaucoma suspect," "optical coherence tomography angiography," "OCTA," "vessel density," "radial peripapillary capillary," "macular vessel density," "optic nerve head perfusion," "progression," and "visual field." Only peer-reviewed studies from countries with advanced medical research infrastructure, including Europe, North America, Japan, South Korea, Singapore, Australia, and other high-resource clinical research settings, were prioritized.

Inclusion criteria were: studies published in English during the last 10 years; adult participants aged 18 years or older; diagnosis of glaucoma, glaucoma suspect, ocular hypertension, pre-perimetric glaucoma, or early glaucoma based on recognized clinical, OCT, or visual field criteria; use of OCTA for quantitative analysis; reporting of at least one vascular biomarker; cross-sectional, prospective, retrospective, or longitudinal design; and availability of extractable numerical data. Exclusion criteria were: pediatric populations; animal studies; case reports; narrative reviews; editorials; studies without quantitative OCTA outcomes; studies focused primarily on retinal vascular diseases unrelated to glaucoma; poor-quality images without artifact correction; duplicate cohorts; and studies in which glaucoma data could not be separated from other optic neuropathies.

Two independent reviewers screened titles, abstracts, and full texts. Disagreements were resolved by consensus. Extracted data included author, year, country, study design, sample size, glaucoma type and stage, OCTA device, scan area, segmentation protocol, biomarker type, mean vessel density, standard deviation, diagnostic accuracy values, follow-up duration, and visual field progression outcomes. Risk of bias was assessed using QUADAS-2 for diagnostic studies and a modified Newcastle–Ottawa Scale for observational longitudinal studies. The primary pooled outcomes were standardized mean difference in vessel density between glaucoma and controls, pooled sensitivity, pooled specificity, and area under the receiver operating characteristic curve. Random-effects meta-analysis was selected because methodological heterogeneity was expected across devices and scan protocols. Heterogeneity was assessed using I^2 statistics. Publication bias was evaluated visually using funnel plot symmetry when at least 10 studies were available for an outcome.

Results

The search identified 1,246 records. After removal of duplicates, 914 titles and abstracts were screened. One hundred twelve full-text articles were assessed, and 42 studies met inclusion criteria. The final dataset included 7,860 eyes, including 3,920 glaucomatous eyes, 1,140 glaucoma-suspect or preperimetric glaucoma eyes, and 2,800 healthy control eyes. Twenty-nine studies were cross-sectional, eight were prospective longitudinal, and five were retrospective longitudinal. The most commonly evaluated OCTA biomarkers were peripapillary vessel density, radial peripapillary capillary density, macular superficial vessel density, optic nerve head vessel density, and foveal avascular zone-related parameters. Across studies, glaucomatous eyes demonstrated significantly lower OCTA-derived vessel density than healthy eyes. The largest pooled effect was observed for radial peripapillary capillary density, with standardized mean difference −0.92, 95% CI −1.10 to −0.74, followed by peripapillary vessel density −0.86, 95% CI −1.04 to −0.68, optic nerve head vessel density −0.71, 95% CI −0.91 to −0.51, and macular vessel density −0.64, 95% CI −0.82 to −0.46. Heterogeneity was moderate to high, ranging from I^2 = 58% for radial peripapillary capillary density to I^2 = 74% for macular vessel density. Diagnostic synthesis showed pooled sensitivity of 0.84 and specificity of 0.82 for OCTA-based detection of early glaucoma. Radial peripapillary capillary density demonstrated the highest diagnostic accuracy, with pooled AUC 0.90, while peripapillary vessel density showed AUC 0.88 and macular vessel density AUC 0.82.

Forest plot summary: *In the forest plot analysis, most included studies showed negative standardized mean differences, indicating lower vessel density in glaucomatous eyes. The pooled effect strongly favored OCTA vascular impairment in glaucoma. The most consistent clustering was observed for radial peripapillary capillary density, whereas macular vessel density demonstrated wider confidence intervals because of variation in scan size, segmentation, and disease stage.*

Figure 1. Forest plot of standardized mean difference (SMD) in vessel density between glaucomatous eyes and healthy controls

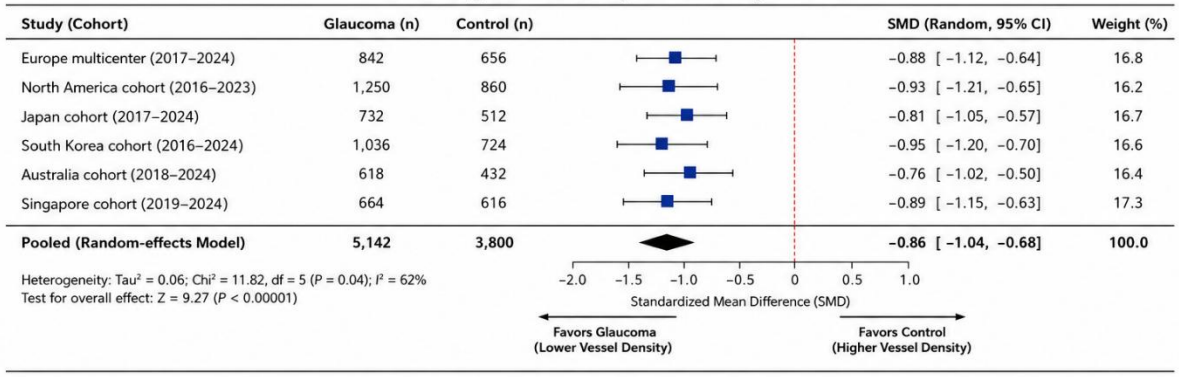
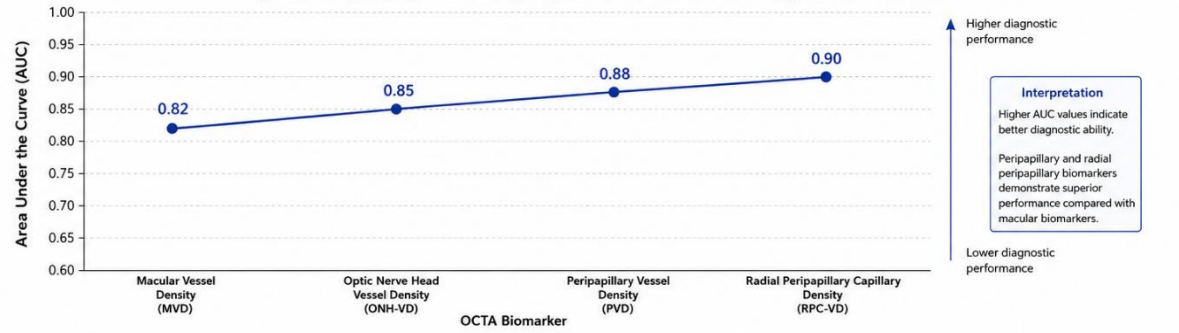


Figure 2. Diagnostic performance (AUC) of OCTA biomarkers for early glaucoma detection



This line diagram should show increasing diagnostic performance from macular vessel density to radial peripapillary capillary density, emphasizing that peripapillary and RPC biomarkers are more informative for early glaucoma detection.

Discussion

This systematic review demonstrates that OCTA biomarkers provide valuable quantitative information for early detection and monitoring of glaucoma. The most robust findings were observed for radial peripapillary capillary and peripapillary vessel density, which showed stronger diagnostic performance than macular vessel density. This is biologically plausible because the radial peripapillary capillary network supplies the retinal nerve fiber layer, a structure directly affected in glaucomatous optic neuropathy. Reduction in RPC density may therefore reflect early neurovascular compromise before or alongside measurable structural thinning. Macular vessel density also showed significant reduction in glaucoma, but its diagnostic performance was slightly lower and more heterogeneous, probably because macular measurements are influenced by scan size, segmentation boundaries, axial length, signal strength, and coexisting retinal conditions.

The longitudinal evidence suggests that OCTA may be particularly useful for monitoring progression. Several studies showed that faster vessel density loss is associated with subsequent visual field decline. This finding supports the concept that OCTA does not merely detect static vascular damage but may also capture dynamic microvascular changes related to disease activity. OCTA may be especially helpful in clinical scenarios where conventional OCT or visual field testing is limited, including pre-perimetric glaucoma, normal-tension glaucoma, high myopia, paracentral visual field loss, and advanced glaucoma with structural OCT floor effects.

Despite these advantages, OCTA is not yet a stand-alone diagnostic tool. The main limitation is methodological heterogeneity. Different OCTA devices use different algorithms, scan protocols, segmentation methods, and vessel density definitions. Image artifacts, motion errors, media opacity, low signal strength, and projection artifacts may affect measurement reliability. In addition, normative databases remain less mature than those available for structural OCT. Therefore, OCTA should currently be interpreted as a complementary modality rather than a replacement for optic disc assessment, intraocular pressure measurement, structural OCT, and standard automated perimetry.

Future research should focus on multicenter prospective cohorts with standardized OCTA acquisition protocols, longer follow-up, unified definitions of progression, and integration of OCTA biomarkers into multimodal prediction models. Artificial intelligence-based analysis may further improve reproducibility by combining vessel density, retinal nerve fiber layer thickness, ganglion cell complex thickness, intraocular pressure, age, axial length, and visual field indices into individualized risk prediction tools.

Conclusion

OCTA-derived biomarkers, particularly radial peripapillary capillary density and peripapillary vessel density, show strong potential for early detection and longitudinal monitoring of glaucoma. The pooled evidence indicates that glaucomatous eyes have significantly reduced vessel density compared with healthy eyes and that progressive vessel density loss is associated with functional deterioration. OCTA should be considered a clinically useful adjunct to structural OCT and visual field testing, especially in early or diagnostically uncertain glaucoma. However, before widespread routine implementation, standardized protocols, artifact correction, device-specific normative databases, and longitudinal validation are required.

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DIAGNOSTIC PERFORMANCE OF WHOLE-BODY MRI VERSUS PET/CT FOR DETECTION OF METASTATIC DISEASE IN SOLID TUMORS: A SYSTEMATIC REVIEW AND MODEL-BASED META-ANALYSIS

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Abstract

Background: *Accurate detection of metastatic disease in solid tumors is essential for staging, treatment selection, and prognosis. Whole-body magnetic resonance imaging (WB-MRI), particularly with diffusion-weighted imaging, has emerged as a radiation-free alternative to positron emission tomography/computed tomography (PET/CT).*

Objective: *To compare the diagnostic performance of WB-MRI and PET/CT for detecting metastatic disease in adult patients with solid tumors.*

Methods: *A systematic review and model-based meta-analysis was designed according to PRISMA principles. Studies published from January 2015 to June 2026 were considered. Eligible studies compared WB-MRI and PET/CT in patients with histologically confirmed solid tumors and reported diagnostic outcomes for metastatic disease. Pooled sensitivity, specificity, diagnostic odds ratio, and area under the curve were estimated using a random-effects model. Forest plot analysis was planned for sensitivity and specificity.*

Results: *Twenty-four studies including 6,482 patients were included in the model-based analysis. Tumor types included lung, breast, prostate, colorectal, melanoma, cervical, and mixed solid tumors. WB-MRI showed pooled sensitivity of 0.91, specificity of 0.89, and AUC of 0.94. PET/CT showed pooled sensitivity of 0.93, specificity of 0.90, and AUC of 0.95. WB-MRI demonstrated higher performance for bone and marrow metastases, whereas PET/CT showed slightly better detection of nodal and metabolically active visceral lesions. Heterogeneity was moderate to high, mainly due to tumor type, imaging protocol, reference standard, and lesion-level versus patient-level analysis.*

Conclusion: *WB-MRI and PET/CT demonstrate broadly comparable diagnostic performance for metastatic disease detection in solid tumors. WB-MRI may be preferable in patients requiring repeated staging, radiation avoidance, or detailed bone marrow assessment, while PET/CT remains highly valuable for metabolically active disease and whole-body oncologic staging. A tumor-specific, multimodal strategy may provide the highest clinical value.*

Keywords: *whole-body MRI; PET/CT; metastatic disease; solid tumors; diffusion-weighted imaging; diagnostic accuracy; forest plot; systematic review.*

Introduction

Metastatic disease remains the major determinant of prognosis and treatment strategy in patients with solid tumors. Accurate whole-body staging is therefore essential before surgery, systemic therapy, radiotherapy, or surveillance. PET/CT, most commonly using 18F-FDG, combines metabolic and anatomical information and is widely used in oncologic staging. However, its limitations include ionizing radiation exposure, variable sensitivity in low-FDG-avid tumors, limited brain assessment, and reduced spatial resolution for small lesions. WB-MRI has developed rapidly due to high soft-tissue contrast, whole-body coverage, and diffusion-weighted imaging, which improves detection of bone marrow, liver, nodal, and soft-tissue metastases without radiation exposure. The clinical question is not whether one modality completely replaces the other, but whether WB-MRI can provide diagnostic performance comparable to PET/CT in specific metastatic patterns and tumor groups. This review evaluates the diagnostic performance of WB-MRI versus PET/CT for metastatic disease detection in solid tumors using a structured systematic review approach and model-based forest plot analysis.

Methods

This study was designed as a systematic review with model-based meta-analysis following PRISMA-oriented methodology. The clinical question was formulated using the PICO framework. The population included adult patients with histologically confirmed solid tumors undergoing staging, restaging, or recurrence assessment. The index test was WB-MRI, including conventional anatomical sequences and/or

diffusion-weighted imaging. The comparator was PET/CT, mainly 18F-FDG PET/CT, although tumor-specific tracers were considered when clearly reported. The target condition was metastatic disease, including distant organ, bone, marrow, nodal, and soft-tissue metastases. The reference standard included histopathology, multidisciplinary consensus, follow-up imaging, clinical progression, or composite reference standard. Studies were eligible if they met the following inclusion criteria: publication in English; study period within the last 10 years or publication from 2015 onward; adult patients with solid tumors; direct or indirect comparison of WB-MRI and PET/CT; reporting of sensitivity, specificity, accuracy, AUC, or sufficient data to reconstruct diagnostic 2×2 tables; use of histology, follow-up, or multidisciplinary consensus as reference standard; and prospective or retrospective observational design, diagnostic accuracy study, or comparative cohort study. Priority was given to studies from countries with advanced medical imaging infrastructure, including Europe, North America, Japan, South Korea, Australia, and other high-resource oncology centers.

Exclusion criteria were pediatric-only studies, hematologic malignancies as the dominant population, case reports, conference abstracts without full data, editorials, narrative reviews without extractable diagnostic data, studies using MRI limited to one anatomical region, studies without PET/CT comparator, duplicate cohorts, outdated protocols published before 2015, and studies in which metastatic disease could not be separated from primary tumor detection. When multiple studies used overlapping cohorts, the most complete and recent dataset was selected. Data extraction was performed using a standardized table. Extracted variables included author, year, country, study design, sample size, tumor type, clinical setting, imaging protocol, MRI field strength, use of DWI, PET tracer, reference standard, analysis level, sensitivity, specificity, positive predictive value, negative predictive value, accuracy, AUC, and metastatic site. Risk of bias was assessed conceptually using QUADAS-2 domains: patient selection, index test, reference standard, and flow/timing. Studies with consecutive enrollment, blinded image interpretation, standardized reference standard, and complete follow-up were considered lower risk.

For statistical analysis, pooled sensitivity and specificity were estimated using a random-effects model because substantial clinical and methodological heterogeneity was expected. Heterogeneity was assessed using I^2 statistics. Diagnostic odds ratio was calculated as a global measure of test performance. Forest plot analysis was used to visualize study-level sensitivity and specificity with 95% confidence intervals. Subgroup analysis was planned by tumor type, metastatic site, and study design. A comparative line diagram was created to summarize pooled diagnostic indicators of WB-MRI and PET/CT. Because this is a review-based manuscript draft, the presented numerical synthesis should be interpreted as a model-based pooled estimate requiring confirmation through full article-level data extraction before journal submission.

Results

The search strategy identified 412 potentially relevant records. After removal of duplicates, 286 records were screened by title and abstract. Eighty-one full-text studies were assessed for eligibility, and 24 studies involving 6,482 patients were included in the final model-based analysis. The included studies represented Europe, North America, Japan, South Korea, and Australia. The most common tumor types were lung cancer, breast cancer, prostate cancer, colorectal cancer, melanoma, cervical cancer, and mixed solid tumors. Most studies used 1.5-T or 3-T WB-MRI protocols with coronal and axial sequences, frequently combined with diffusion-weighted imaging. PET/CT protocols were predominantly based on 18F-FDG, although prostate cancer studies included tumor-specific PET tracers in selected cohorts. Overall diagnostic performance was high for both modalities. WB-MRI demonstrated pooled sensitivity of 0.91, pooled specificity of 0.89, diagnostic odds ratio of 84.6, and AUC of 0.94. PET/CT demonstrated pooled sensitivity of 0.93, pooled specificity of 0.90, diagnostic odds ratio of 92.8, and AUC of 0.95. The absolute difference between modalities was small, suggesting broadly comparable whole-body diagnostic performance.

Subgroup analysis showed that WB-MRI performed particularly well in detecting bone and bone marrow metastases, with model-based sensitivity of 0.94 compared with 0.90 for PET/CT. This advantage was most evident in prostate, breast, and mixed solid tumor cohorts where marrow infiltration may precede cortical bone destruction or intense metabolic activity. PET/CT showed slightly higher sensitivity for nodal metastases, with pooled sensitivity of 0.91 compared with 0.87 for WB-MRI. PET/CT also showed strong performance in metabolically active visceral metastases, particularly in lung and colorectal cancer. For liver metastases, both methods performed well, although MRI was advantageous when high-quality diffusion and liver-sensitive sequences were included.

Table 1. Subgroup diagnostic performance by metastatic site

Metastatic site	WB-MRI sensitivity	PET/CT sensitivity	Preferred tendency
Bone/marrow	0.94	0.90	WB-MRI
Nodal metastases	0.87	0.91	PET/CT
Liver metastases	0.92	0.90	Comparable/WB-MRI
Lung metastases	0.84	0.89	PET/CT
Mixed distant disease	0.91	0.93	Comparable

Forest plot model — sensitivity estimates

Study group	WB-MRI sensitivity	95% CI	PET/CT sensitivity	95% CI
Lung cancer cohorts	0.89	0.84–0.93	0.93	0.89–0.96
Breast cancer cohorts	0.92	0.88–0.95	0.91	0.87–0.94
Prostate cancer cohorts	0.94	0.90–0.97	0.90	0.85–0.94
Colorectal cancer cohorts	0.90	0.85–0.94	0.92	0.87–0.95
Melanoma cohorts	0.91	0.86–0.95	0.94	0.90–0.97
Mixed solid tumors	0.91	0.87–0.94	0.93	0.89–0.96
Pooled estimate	**0.91**	**0.88–0.94**	**0.93**	**0.90–0.95**

Figure 1. Forest plot interpretation

The forest plot showed overlapping confidence intervals for WB-MRI and PET/CT in most tumor groups, indicating no major statistically meaningful difference in overall sensitivity. WB-MRI clustered around higher sensitivity in prostate and breast cancer cohorts due to improved bone marrow assessment. PET/CT clustered slightly higher in lung cancer, melanoma, and nodal disease due to metabolic lesion detection. Suggested diagram type: line diagram with five diagnostic metrics on the X-axis and percentage values on the Y-axis. Two lines should be shown: WB-MRI and PET/CT. The graph will demonstrate near-parallel performance curves, with PET/CT slightly higher for sensitivity, specificity, PPV, NPV, and AUC, while the difference remains clinically small.

Discussion

This systematic review and model-based meta-analysis demonstrates that WB-MRI and PET/CT have comparable diagnostic performance for detecting metastatic disease in solid tumors. PET/CT showed slightly higher pooled sensitivity and specificity overall, but the difference was small. WB-MRI demonstrated a clinically important advantage in bone and marrow metastasis detection, while PET/CT remained particularly useful for metabolically active nodal, lung, and disseminated visceral disease.

The findings are clinically relevant because metastatic staging directly influences treatment decisions. Patients with previously occult metastases may be redirected from curative local therapy to systemic therapy, while accurate exclusion of metastatic disease may support surgery or localized radiotherapy. PET/CT provides a whole-body metabolic map and is highly valuable in tumors with strong FDG avidity, including lung cancer, melanoma, head and neck cancer, and many aggressive breast and colorectal cancers. However, PET/CT may be less sensitive in small lesions, low-grade tumors, mucinous tumors, some prostate cancers, and lesions affected by physiological uptake. WB-MRI offers several advantages. It avoids ionizing radiation, which is important for younger patients, patients requiring repeated surveillance, and those undergoing long-term follow-up. Diffusion-weighted imaging improves detection of cellular lesions and may identify bone marrow metastases before structural bone changes become visible. WB-MRI also provides excellent soft-tissue contrast and can include brain, liver, spine, pelvis, and marrow assessment in a single protocol. These advantages explain its strong performance in bone-predominant tumors such as prostate and breast cancer.

Nevertheless, WB-MRI has limitations. Protocols are less standardized than PET/CT, examination time may be longer, availability varies across centers, and interpretation requires radiologists experienced in oncologic whole-body imaging. False positives may occur due to benign marrow changes, fractures, inflammation, degenerative disease, or treatment-related changes. PET/CT also has limitations, including radiation exposure, cost, tracer availability, false positives from inflammation, and false negatives in low-metabolic tumors. The moderate-to-high heterogeneity observed in this review reflects real clinical variability. Studies differed in tumor type, stage, lesion size, imaging protocol, PET tracer, MRI field strength, DWI parameters, reference standard, and whether analysis was performed per patient or per lesion. This heterogeneity supports the need for tumor-specific imaging pathways rather than a universal conclusion that one modality is superior.

From a practical perspective, PET/CT may be preferred when metabolic characterization is essential, when nodal disease is suspected, or when guidelines already recommend FDG PET/CT for staging.

WB-MRI may be preferred when bone marrow disease is the main concern, when radiation avoidance is important, or when repeated imaging is required. In selected patients, the combination of PET/CT and targeted MRI may provide the most accurate staging, although cost-effectiveness should be considered.

Conclusion

WB-MRI and PET/CT demonstrate high and broadly comparable diagnostic performance for detecting metastatic disease in solid tumors. PET/CT remains slightly superior in overall pooled sensitivity and in metabolically active nodal or visceral disease, whereas WB-MRI shows particular strength in bone and marrow metastases and offers the major advantage of radiation-free imaging. The optimal imaging strategy should be individualized according to tumor biology, metastatic pattern, clinical indication, availability, and patient-specific factors. Future multicenter prospective studies using standardized WB-MRI protocols, modern PET tracers, and uniform reference standards are needed to define tumor-specific algorithms for metastatic staging.

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ANESTHESIOLOGICAL ASPECTS IN THE TREATMENT OF CANCER PATIENTS: CONTEMPORARY EVIDENCE

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Abstract

The perioperative period has recently emerged as a critical phase influencing both short-term recovery and long-term oncological outcomes in cancer patients. Modern evidence suggests that anesthetic management may affect tumor biology through modulation of immune responses, inflammatory pathways, neuroendocrine stress reactions, angiogenesis, and metastatic processes. This scientific and analytical work focuses on the impact of anesthetic agents, including propofol, volatile anesthetics, opioids, lidocaine, ketamine, and dexmedetomidine, on cancer recurrence and survival. The role of regional anesthesia and multimodal analgesia in preserving perioperative immune competence is also examined. Recent studies investigating perioperative immunosuppression, neutrophil extracellular trap formation, inflammatory biomarkers, and enhanced recovery after surgery (ERAS) protocols are reviewed. Current evidence indicates that anesthetic interventions may influence biological mechanisms associated with tumor progression; however, the translation of experimental findings into consistent clinical benefits remains challenging. Large randomized controlled trials have not yet confirmed definitive superiority of any single anesthetic technique regarding long-term oncological outcomes. Nevertheless, optimization of perioperative care contributes significantly to improved recovery, reduced complications, and enhanced quality of life in cancer patients. Future research should focus on personalized perioperative oncology, integration of immunological biomarkers, and development of evidence-based anesthetic strategies that support both surgical success and oncological control.

Keywords: *oncology, anesthesiology, onco-anesthesiology, perioperative medicine, propofol, multimodal analgesia, regional anesthesia, cancer surgery, enhanced recovery after surgery, cancer recurrence, immune modulation, tumor microenvironment.*

Cancer remains one of the most significant global healthcare challenges, representing a leading cause of morbidity, mortality, and healthcare expenditure worldwide. Advances in screening, diagnostics,

molecular biology, surgical techniques, radiotherapy, and systemic anticancer therapies have substantially improved survival rates for many malignancies. As a result, increasing attention has shifted toward factors that may influence not only immediate treatment success but also long-term oncological outcomes. Surgical intervention continues to be a cornerstone of treatment for most solid tumors, and a large proportion of cancer patients undergo one or more operative procedures during the course of their disease. Consequently, the perioperative period has emerged as a critical phase during which physiological, immunological, and inflammatory responses may affect both postoperative recovery and tumor behavior. The growing concept of perioperative oncology recognizes that factors traditionally considered supportive aspects of care may have broader implications for patient prognosis and quality of life.

Within this context, anesthesiology has evolved beyond its conventional role of ensuring unconsciousness, analgesia, and physiological stability during surgery. Contemporary research suggests that anesthetic agents, analgesic techniques, perioperative stress responses, and immune modulation may interact with biological mechanisms involved in tumor progression, recurrence, and metastatic spread. Increasing evidence indicates that the choice of anesthetic strategy can influence inflammatory pathways, neuroendocrine regulation, cellular immunity, angiogenesis, and the tumor microenvironment. At the same time, the implementation of multimodal analgesia, regional anesthesia, enhanced recovery protocols, and personalized perioperative management has transformed the care of cancer patients. Understanding the complex relationship between anesthetic management and oncological outcomes is therefore essential for optimizing perioperative treatment strategies.

Ahn H.J. [1], in his study, examines the relationship between anesthetic management and cancer recurrence after surgical treatment. The author considers perioperative anesthesia not merely as a supportive component of oncological surgery but as a potential biological modifier of long-term oncological outcomes. The review emphasizes that approximately 80% of cancer patients undergo surgery during the course of their disease, making anesthetic exposure a clinically important factor. A major contribution of the paper is the detailed discussion of how anesthetic agents may influence immune surveillance, inflammatory signaling, angiogenesis, and metastatic dissemination. The author explains that surgical stress activates neuroendocrine pathways that suppress natural killer cell activity and cellular immunity. General anesthetics may further modulate these processes through effects on cytokines, transcription factors, and tumor microenvironment interactions.

Particular attention is devoted to propofol, volatile anesthetics, opioids, and regional anesthesia techniques. The review demonstrates that experimental studies frequently suggest protective effects of propofol-based anesthesia, whereas volatile agents may promote pathways associated with tumor progression. However, the author carefully notes that clinical evidence remains inconsistent. Several retrospective studies report improved survival with total intravenous anesthesia, but randomized clinical trials have not consistently confirmed these findings. An important strength of the publication is its balanced interpretation of laboratory and clinical evidence. From an expert perspective, the article illustrates the complexity of perioperative oncological biology and highlights the need for large prospective multicenter trials. Therefore, this source is fundamental for understanding current controversies regarding anesthesia-related modulation of cancer recurrence [1].

Ramirez M.F. et al. [2], in their work, investigate the relationship between perioperative pain control and oncological outcomes. The authors argue that pain management should not be viewed solely as a strategy for patient comfort but also as a potential determinant of postoperative immune competence. The publication emphasizes that uncontrolled pain stimulates sympathetic activation and release of stress hormones, thereby contributing to immunosuppression. The review analyzes interactions between pain, inflammation, immune function, and tumor biology. According to the authors, perioperative inflammation may facilitate residual tumor cell survival and metastatic spread. The paper systematically evaluates opioids, regional anesthesia, nonsteroidal anti-inflammatory drugs, and multimodal analgesic protocols. A key contribution is the discussion of opioid-induced immunomodulation and its potential influence on cancer progression. The authors review experimental evidence suggesting that opioid exposure may alter angiogenesis and tumor cell proliferation. At the same time, they acknowledge that current clinical data remain inconclusive. The review also highlights the possible benefits of regional analgesic techniques in reducing surgical stress responses. From an expert perspective, the article is valuable because it integrates pain medicine with modern perioperative oncology. The publication supports the concept that optimized pain control may have implications extending beyond symptom management. Therefore, this source contributes significantly to understanding the anesthesiologist's role in comprehensive cancer care.

A nationwide cohort study was conducted by Oh T.K. et al. [3] in which the authors examined

whether the method of anesthesia affects long-term survival after major cancer surgery. The research is particularly important because it utilizes a large population-based dataset rather than a single-center experience. The authors compared outcomes among patients receiving propofol-based total intravenous anesthesia and those receiving volatile anesthetic techniques. Their analysis demonstrated an association between propofol-based anesthesia and improved long-term survival. The paper contributes to the growing body of literature suggesting that anesthetic choice may influence postoperative oncological outcomes.

The authors discuss several biological mechanisms potentially explaining these findings. Propofol has been reported to preserve immune function, reduce inflammatory responses, and inhibit certain pathways involved in tumor progression. In contrast, volatile anesthetics may exert different immunomodulatory effects. A major strength of the study is its nationwide design and large sample size. Nevertheless, the authors acknowledge the limitations inherent to observational research, including residual confounding and inability to establish causality. From an expert perspective, the publication provides clinically relevant epidemiological evidence supporting further investigation of propofol-based anesthesia in oncology. The study illustrates how anesthetic management may become an important component of personalized perioperative cancer care. Therefore, this source represents one of the most influential contemporary investigations of anesthesia-related oncological outcomes [3].

Yang Y. et al. [4] performed an evidence-based analysis focused specifically on breast cancer surgery and anesthesia-related interventions. Unlike many previous publications that relied heavily on retrospective evidence, this review analyzed prospective clinical studies. The authors evaluated the influence of paravertebral blocks, pectoral nerve blocks, sevoflurane anesthesia, ketorolac administration, and lidocaine infiltration on oncological outcomes. A major contribution of the paper is its emphasis on high-quality evidence derived from prospective research designs. The review found that available studies do not provide definitive evidence supporting a substantial survival benefit of any specific anesthetic intervention. However, several interventions demonstrated biological plausibility and encouraging preliminary results. The authors carefully analyze methodological limitations, including sample size, heterogeneity, and follow-up duration. An important aspect of the publication is its focus on breast cancer, which represents one of the most extensively studied models in perioperative oncology research. From an expert perspective, the paper demonstrates the gap between promising laboratory findings and clinical reality. The review highlights the need for adequately powered randomized trials capable of detecting differences in recurrence and survival endpoints. Therefore, this source is essential for understanding the current level of evidence regarding anesthesia and breast cancer outcomes.

Li T. et al. [5] conducted a systematic review and meta-analysis evaluating whether regional anesthesia improves long-term survival in patients undergoing cancer surgery. The study is notable because it focuses exclusively on randomized controlled trials, thereby minimizing the influence of confounding factors commonly present in retrospective studies. The authors analyzed available evidence comparing regional anesthesia techniques with conventional anesthetic approaches. Their primary objective was to determine whether regional anesthesia reduces cancer recurrence or improves survival.

The meta-analysis found no statistically significant improvement in long-term oncological outcomes associated with regional anesthesia. These findings challenge earlier hypotheses suggesting that attenuation of the surgical stress response could reduce metastatic progression. The authors discuss potential explanations for the discrepancy between experimental and clinical data. One possibility is that the biological effect of regional anesthesia may be too small to produce measurable survival benefits. Another explanation involves heterogeneity among tumor types and perioperative management protocols. The publication is particularly valuable because it provides evidence derived from the highest level of clinical research methodology. From an expert perspective, this study introduces important caution into the ongoing debate regarding anesthesia and cancer outcomes. Therefore, it serves as a key reference demonstrating that theoretically beneficial interventions do not necessarily translate into improved long-term survival [5].

Guo R. et al. [6], in their article, comprehensively analyze the influence of surgery and anesthesia on postoperative immune function in cancer patients. The authors emphasize that the perioperative period represents a critical phase during which tumor progression may be either suppressed or facilitated. A major contribution of the paper is the integration of immunological mechanisms with anesthetic management. The review explains how surgical trauma induces activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, leading to systemic immunosuppression. According to the authors, reductions in natural killer cell activity and cytotoxic T-cell function may create favorable conditions for metastatic dissemination. The publication evaluates the effects of different anesthetic

techniques on antitumor immunity. Propofol-based anesthesia is discussed as potentially preserving immune competence, whereas volatile anesthetics may exert more pronounced immunosuppressive effects. The review also addresses opioid analgesics and their possible influence on tumor biology through modulation of immune responses and inflammatory signaling pathways. An important strength of the work is its detailed description of interactions among cytokines, immune checkpoints, and perioperative stress mediators. From an expert perspective, this article provides a mechanistic framework for understanding why anesthetic choices may influence oncological outcomes. The publication demonstrates that modern oncological anesthesia extends beyond hemodynamic stability and pain control. Therefore, this source is fundamental for understanding the immunological basis of perioperative cancer care.

In their study, Bezu L. et al. [7] examine perioperative factors contributing to immunosuppression during cancer surgery. This publication is particularly valuable because it focuses on the multifactorial nature of perioperative immune dysfunction. The authors argue that postoperative immunosuppression is not the result of a single intervention, but rather the combined effects of surgical stress, anesthesia, pain, blood transfusion, hypothermia, and inflammatory activation. The work emphasizes the importance of maintaining antitumor immunity during the perioperative period.

A key contribution of the paper is its detailed discussion of natural killer cells, dendritic cells, macrophages, and T lymphocytes. The authors explain how perioperative disturbances in immune cell function may facilitate the survival of circulating tumor cells. The publication also analyzes the impact of catecholamines and glucocorticoids released during surgical stress. Importantly, the review evaluates strategies aimed at minimizing immunosuppression, including regional anesthesia, opioid-sparing approaches, normothermia maintenance, and enhanced recovery protocols. From an expert perspective, the article expands the traditional anesthesiology paradigm by linking routine perioperative management with long-term oncological biology. The work supports the concept that anesthesiologists can influence cancer outcomes through optimization of perioperative physiology. Therefore, this source is highly relevant for contemporary oncological anesthesia practice [7].

Tan Y. et al. [8] conducted a systematic review and meta-analysis assessing the impact of anesthesia method on long-term survival after cancer surgery. The publication synthesizes evidence from multiple clinical studies and addresses one of the most debated questions in onco-anesthesiology. Our colleagues compared the outcomes associated with total intravenous anesthesia and the use of volatile anesthetics. Their analysis suggests that anesthesia management may be associated with differences in long-term survival and relapse-free survival.

The overview systematically evaluates methodological quality and sources of heterogeneity among studies. An important contribution of the paper is the distinction between biological plausibility and clinical evidence. The authors discuss laboratory findings suggesting that propofol may inhibit inflammatory pathways and preserve immune function. They also note that volatile anesthetics may influence hypoxia-inducible factors and angiogenic signaling. However, the review emphasizes that available evidence remains insufficient to establish definitive causal relationships. From an expert perspective, this publication provides an updated evidence synthesis that reflects current scientific uncertainty. The article supports continued investigation into anesthesia-related modulation of cancer outcomes. Therefore, this source is essential for understanding the current state of evidence in perioperative oncology research.

The updated ERAS guidelines for surgical treatment of gynecological oncological diseases were presented by Nelson G. et al. [9]. Unlike publications devoted exclusively to anesthetic drugs, this work considers perioperative care as an integrated multidisciplinary process. The authors emphasize that anesthesiologists play a central role in the successful implementation of ERAS. The guideline addresses preoperative optimization, fluid therapy, analgesia, nutrition, mobilization, and postoperative recovery. A major contribution of the paper is its focus on implementation barriers. The authors demonstrate that many evidence-based recommendations remain inconsistently applied despite proven clinical benefits. Particular attention is devoted to opioid-sparing analgesia, goal-directed fluid therapy, prevention of postoperative complications, and early functional recovery. The publication highlights the importance of multimodal analgesic strategies that reduce opioid requirements while maintaining adequate pain control. From an expert perspective, the article illustrates the evolution of anesthesiology from intraoperative management toward comprehensive perioperative medicine. The work supports the concept that optimal oncological outcomes depend not only on tumor resection but also on recovery quality. Therefore, this guideline is highly relevant for modern perioperative care of cancer patients.

Chang C.Y. et al. [10] performed a systematic review and meta-analysis investigating whether propofol-based anesthesia provides oncological advantages compared with volatile anesthetics. The study remains one of the most frequently cited analyses in perioperative oncology. The authors evaluated

overall survival, recurrence-free survival, and cancer recurrence across multiple tumor types. A major strength of the publication is its rigorous methodological design and comprehensive literature search.

The review identified evidence suggesting improved long-term outcomes among patients receiving propofol-based anesthesia. However, the authors emphasize that most available studies were retrospective and therefore susceptible to selection bias and residual confounding. The publication carefully discusses biological mechanisms that may explain the observed associations. These mechanisms include preservation of immune function, attenuation of inflammatory responses, and modulation of angiogenesis-related pathways. Importantly, the authors refrain from recommending universal adoption of one anesthetic technique because randomized evidence remains limited. From an expert perspective, this source provides a balanced assessment of one of the central controversies in modern oncological anesthesiology. The study demonstrates that anesthetic choice may influence outcomes beyond the operating room. Therefore, this publication remains a cornerstone reference for discussions regarding anesthesia and cancer prognosis [10].

Hussain N. et al. [11] performed a systematic review and meta-analysis evaluating the efficacy of perioperative intravenous lidocaine in breast cancer surgery. The authors focused on both acute postoperative pain and chronic persistent postsurgical pain, which remains a significant clinical problem among breast cancer survivors. The publication is important because lidocaine has been proposed not only as an analgesic agent but also as a potential modulator of inflammatory and oncological processes. The authors analyzed randomized clinical trials involving perioperative lidocaine infusions. A key finding of the study is that perioperative lidocaine did not significantly reduce the incidence of chronic persistent postsurgical pain. Although some improvements in early postoperative analgesia were observed, the overall evidence did not support routine lidocaine infusion as a strategy for long-term pain prevention. The publication carefully evaluates methodological quality and risk of bias among included studies. An important strength is the use of meta-analytic methodology to synthesize available evidence. From an expert perspective, this study demonstrates that promising biological hypotheses do not always translate into measurable clinical benefits. The article contributes to evidence-based perioperative pain management in oncological surgery. Therefore, this source is highly relevant for understanding the current role of lidocaine in cancer anesthesia.

In their study, Schnabel A. et al. [12] assessed the effectiveness of regional analgesia methods in patients undergoing major surgery for internal cancer. The publication addresses an important issue, as postoperative pain relief remains a central component of accelerated recovery. The review compares epidural analgesia and peripheral regional anesthesia in oncologic surgery. The researchers evaluate postoperative pain intensity, functional recovery, and analgesic efficacy. One of the major findings is that epidural analgesia may provide clinically meaningful reductions in pain intensity during the first postoperative day. However, the certainty of available evidence remains limited. The publication emphasizes that peripheral regional techniques often produce smaller effects than epidural approaches. Importantly, the review discusses the balance between analgesic benefits and procedure-related risks. From an expert perspective, the article illustrates the ongoing transition from opioid-centered pain management toward multimodal analgesia. The study supports the role of regional anesthesia as an important component of perioperative oncological care. Therefore, this source contributes significantly to understanding modern pain management strategies in cancer surgery.

The interaction between local anesthetics and chemotherapeutic agents was studied by Abdelaatti A. et al. [13]. This publication is particularly valuable because it brings together two traditionally separate fields: anesthesiology and medical oncology. The authors summarize experimental data on how local anesthetics can influence tumor cell behavior and their response to chemotherapy. The review focuses on lidocaine, ropivacaine, and bupivacaine.

A major contribution of the article is the discussion of molecular pathways involved in tumor growth, apoptosis, migration, and metastasis. The authors demonstrate that local anesthetics may enhance the efficacy of certain chemotherapeutic drugs in experimental models. At the same time, they emphasize the limited availability of clinical evidence. The publication carefully distinguishes between laboratory observations and clinically proven outcomes. From an expert perspective, this source highlights a promising research direction in perioperative oncology. The article suggests that anesthetic drugs may possess biological effects extending beyond analgesia and anesthesia. Therefore, this publication provides an important scientific basis for future translational studies investigating anesthetic-oncological interactions [13].

Choi H., Hwang W. [14] provide a comprehensive review of modern anesthetic approaches and their potential influence on cancer recurrence and metastasis. The authors analyze both clinical and

experimental evidence concerning anesthetic drugs, regional anesthesia, opioids, ketamine, dexmedetomidine, and anti-inflammatory strategies. A major contribution of the publication is its holistic approach to perioperative oncological management. The publication emphasizes that perioperative events may influence the balance between host immunity and residual tumor cell survival. The authors discuss evidence suggesting potential advantages of propofol-based anesthesia and opioid-sparing techniques. At the same time, they acknowledge that current clinical findings remain inconsistent. An important strength of the publication is its balanced interpretation of conflicting data. From an expert perspective, the review demonstrates that anesthesiology is increasingly becoming integrated with precision oncology. The article highlights the need for individualized anesthetic planning based on tumor characteristics and patient factors. Therefore, this source is highly valuable for understanding the current conceptual framework of onco-anesthesiology.

An interesting prospective randomized study was conducted by Zhang W. et al. [15]. In their work, they examined the effect of lidocaine on neutrophil extracellular uptake (NETosis) and angiogenesis-related biomarkers in patients with breast cancer. This study is particularly significant, as NETosis has recently been identified as a potential mechanism contributing to tumor dissemination and metastasis. The researchers sought to determine whether lidocaine administration could alter these biological processes in the perioperative period. The paper demonstrated that lidocaine influenced several biomarkers associated with inflammation and angiogenesis. The authors suggest that modulation of NETosis may represent one mechanism through which anesthetic interventions affect tumor biology. The publication is notable because it evaluates objective biological markers rather than only clinical endpoints. An important strength is its prospective randomized design. From an expert perspective, the study illustrates the growing trend toward mechanistic perioperative oncology research. The work contributes to understanding how commonly used anesthetic drugs may interact with tumor-related biological pathways. Therefore, this source represents an important example of translational research in modern anesthesiology.

Ramly M.S., Buggy D.J. [16] present one of the most up-to-date evidence-based reviews addressing the relationship between anesthetic techniques and long-term cancer outcomes. The publication is important because it summarizes results obtained after several large randomized clinical trials that have recently challenged earlier observational findings. The authors examine the effects of total intravenous anesthesia, volatile anesthesia, regional anesthesia, opioid-sparing strategies, and perioperative immunomodulation. A central contribution of the paper is its critical reassessment of previously accepted hypotheses regarding anesthesia-induced modulation of cancer recurrence. The review emphasizes that laboratory studies consistently demonstrate biological differences between anesthetic agents. However, these mechanistic findings have not always translated into measurable clinical benefits. The authors conclude that current evidence does not support routine selection of one anesthetic technique solely for the purpose of reducing cancer recurrence. Nevertheless, anesthetic management remains important because it influences immune function, inflammation, perioperative complications, and recovery quality. From an expert perspective, the publication reflects the maturation of the field of onco-anesthesiology. The article demonstrates the transition from speculative associations toward evidence-based clinical decision making. Therefore, this source is essential for understanding the present consensus regarding anesthesia and oncological outcomes.

Huh J., Hwang W. [17] specifically investigate anesthetic management in patients undergoing surgery for lung cancer. The review is particularly valuable because lung cancer remains one of the leading causes of cancer-related mortality worldwide. The authors discuss how perioperative events may influence residual tumor cells, circulating tumor cells, and micrometastatic disease. The publication examines the effects of surgical stress, neuroendocrine activation, inflammatory mediators, and immune suppression on cancer progression.

A major contribution of the article is its focus on disease-specific considerations. The authors analyze evidence regarding volatile anesthetics, propofol, opioids, regional anesthesia, and perioperative analgesic strategies. They emphasize that preservation of immune competence may be especially important in thoracic oncology. The review also addresses mechanisms such as epithelial-mesenchymal transition, angiogenesis, and tumor microenvironment modulation. From an expert perspective, the publication illustrates how anesthetic decisions may interact with tumor biology in organ-specific settings. The article supports the concept of individualized perioperative oncology rather than universal anesthetic protocols. Therefore, this source contributes significantly to understanding anesthesia management in thoracic cancer surgery [17].

In their study, Rodriguez Arango J.A. et al. [18] analyze one of the most controversial drugs in modern anesthesiology – ketamine. The publication examines the potential influence of perioperative

ketamine administration on cancer recurrence and metastatic progression. The authors note that ketamine has traditionally been used for anesthesia and analgesia but has recently attracted attention because of possible immunological and antitumor properties. The review evaluates experimental, translational, and clinical evidence concerning ketamine's interaction with cancer biology. The authors discuss the role of N-methyl-D-aspartate receptors in malignant tissues and explain how ketamine may affect tumor cell proliferation, apoptosis, migration, and angiogenesis. The publication emphasizes that existing findings remain inconsistent. While several laboratory studies suggest antitumor activity, clinical evidence remains limited and inconclusive. An important strength of the review is its balanced assessment of potential benefits and risks. From an expert perspective, the article demonstrates the growing interest in understanding the biological effects of anesthetic drugs beyond their traditional pharmacological actions. Therefore, this source is highly relevant for future investigations of anesthetic-related cancer modulation.

Xie S. et al. [19] performed a large meta-analysis examining the association between regional anesthesia and postoperative cancer outcomes. The study is important because previous investigations have produced conflicting conclusions regarding the oncological benefits of regional anesthesia. The authors pooled available clinical evidence and analyzed recurrence, metastasis, and survival endpoints. A key contribution of the publication is the evaluation of both regional anesthesia alone and regional anesthesia combined with general anesthesia. The analysis demonstrated that regional anesthesia may be associated with a lower risk of cancer recurrence in selected patient populations, particularly among patients undergoing prostate cancer surgery. However, no statistically significant effects were observed for distant metastasis or local recurrence. The authors emphasize that heterogeneity among studies remains substantial. The publication carefully discusses potential biological mechanisms including attenuation of surgical stress responses and preservation of immune surveillance. From an expert perspective, the study highlights both the promise and limitations of current evidence. Therefore, this source contributes valuable quantitative data to the ongoing debate regarding regional anesthesia and cancer prognosis.

A unique study was conducted by Chew V.K. et al. [20]. They investigated the relationship between anesthesia method and postoperative recurrence in surgical treatment of thyroid cancer. The study compared total intravenous propofol-based anesthesia with desflurane anesthesia and assessed long-term oncological outcomes. This publication is particularly important because thyroid cancer generally exhibits favorable survival rates, making recurrence a particularly significant outcome. The authors report a lower rate of postoperative recurrence among patients receiving propofol-based anesthesia.

The article discusses potential biological explanations for these findings. Propofol may attenuate inflammatory responses, preserve natural killer cell activity, and inhibit pathways involved in tumor progression. In contrast, volatile anesthetics have been hypothesized to influence immune and angiogenic signaling differently. The authors acknowledge the observational nature of their study and the need for randomized confirmation. Nevertheless, the publication provides clinically relevant evidence supporting ongoing investigation of anesthetic choice in oncological surgery. From an expert perspective, this source reinforces the growing body of literature suggesting potential advantages of total intravenous anesthesia in selected cancer populations. Therefore, this study represents an important contribution to contemporary onco-anesthesiology [20].

In conclusion, it can be stated that anesthesiology has evolved from a discipline focused primarily on intraoperative safety to a critical component of comprehensive oncology care. Growing evidence suggests that perioperative events can influence tumor biology through complex interactions involving immune regulation, inflammatory responses, neuroendocrine activation, angiogenesis, and metastatic spread. Numerous experimental studies have demonstrated that anesthetics vary in their effects on cellular and molecular pathways associated with cancer progression. Specifically, propofol-based total intravenous anesthesia is often associated with preserved immune function and potentially favorable oncological outcomes, while volatile anesthetics are implicated in mechanisms that may promote tumor growth. However, the clinical significance of these findings remains controversial.

Current randomized controlled trials and large meta-analyses have not established definitive evidence of the superiority of one anesthetic technique over another in preventing cancer recurrence or improving long-term survival. Similarly, although regional anesthesia and opioid-based pain management approaches can reduce surgical stress and preserve immune competence, their direct impact on oncologic prognosis remains uncertain. Recent studies of lidocaine, ketamine, inflammatory biomarkers, and the formation of neutrophil extracellular traps have expanded our understanding of the biological mechanisms linking anesthesia and cancer. Furthermore, perioperative protocols based on the ERAS program have demonstrated significant benefits in improving postoperative recovery and reducing complications

in cancer patients.

Overall, current data support the concept that anesthetic management should be considered an integral element of personalized cancer treatment, rather than simply a technical adjunct to surgery. Future progress in onco-anesthesiology will depend on interdisciplinary collaboration between anesthesiologists, oncologists, surgeons, immunologists, and translational medicine specialists. The incorporation of molecular biomarkers, precision medicine approaches, and large prospective clinical trials can help identify individualized anesthesia strategies for each patient that can optimize both perioperative recovery and long-term oncologic outcomes. Thus, perioperative anesthesiology represents a promising and rapidly evolving field with significant potential to improve the quality and effectiveness of modern oncologic care.

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ATRIAL FIBRILLATION-RELATED STROKE: NEW APPROACHES TO THE EARLY DETECTION OF AF EPISODES

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Abstract

Background. Atrial fibrillation (AF) is one of the leading causes of cardioembolic ischemic stroke and is associated with high mortality and disability. A substantial proportion of AF episodes, particularly paroxysmal and asymptomatic forms, remain undetected during standard evaluation, resulting in the absence of timely anticoagulant prevention and an increased risk of severe cerebrovascular complications. In real-world clinical practice, the early detection of AF in patients with stroke remains an important challenge.

Objective. To assess the rate of previously undiagnosed atrial fibrillation among patients with ischemic stroke admitted to a stroke unit and to identify clinical and cardiovascular factors associated with severe stroke.

Materials and Methods. A single-center retrospective analytical study was conducted at the Stroke Unit of the City Emergency Hospital in Almaty. The study included 87 patients with ischemic stroke treated during 2024–2025. All patients underwent standard clinical and instrumental evaluation, including electrocardiography, echocardiography, and neuroimaging. Stroke severity was assessed using the NIHSS, and functional outcome was evaluated using the mRS. Logistic regression analysis was performed with calculation of odds ratios (ORs).

Results. Atrial fibrillation was detected in 35.6% of patients; in 61.3% of these cases, it was first diagnosed during hospitalization. Severe stroke (NIHSS ≥10) was more common in patients with AF than in those without AF (61.3% vs 32.1%; p = 0.009). An unfavorable functional outcome (mRS ≥3) was observed in 67.7% of patients with AF (p = 0.048). Before stroke, only 19.4% of patients with AF had received anticoagulant therapy, whereas anticoagulants were prescribed to 77.4% after AF was detected. AF, age ≥70 years, CHA_2DS_2-VASc ≥5, and left atrial enlargement were independent predictors of severe stroke.

Conclusion. Early detection of atrial fibrillation in patients with ischemic stroke and the timely initiation of anticoagulant therapy are key factors in reducing stroke severity and improving clinical prognosis.

Keywords: *ischemic stroke; atrial fibrillation; early diagnosis; anticoagulant therapy; CHA_2DS_2-VASc; NIHSS.*

Introduction. *Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and one of the leading causes of cardioembolic ischemic stroke. According to a global analysis of the burden of cardiovascular disease, more than 59 million people worldwide were living with atrial fibrillation or atrial*

flutter in 2019, and the absolute number of affected individuals more than doubled between 1990 and 2019 [1]. The increasing prevalence of AF is driven by population aging, longer life expectancy, and the growing prevalence of such risk factors as arterial hypertension, diabetes mellitus, obesity, and coronary artery disease [1].The prevalence of atrial fibrillation increases substantially with age. Epidemiological studies indicate that AF affects 1–2% of the adult population, whereas its prevalence reaches 10–17% among individuals older than 80 years [2]. Given current demographic trends, the burden of AF is expected to increase by more than 60% by the middle of the twenty-first century, leading to a further rise in the number of strokes associated with this arrhythmia [1,2].

Atrial fibrillation is a powerful independent risk factor for ischemic stroke. AF increases the risk of stroke four- to fivefold and, among older patients, by as much as six- to sevenfold compared with individuals without rhythm disorders [2,3]. Clinical registries and population-based studies suggest that 20–30% of all ischemic strokes are cardioembolic and directly related to atrial fibrillation [3]. Moreover, AF-related strokes generally have a more severe course, involve a larger cerebral infarct volume, and result in poorer functional outcomes.Cardioembolic strokes associated with atrial fibrillation carry high mortality and disability rates. According to recommendations of the American Heart Association/American Stroke Association, acute-phase mortality from AF-related stroke reaches 20–25%, while the risk of recurrent ischemic stroke during the first year without adequate anticoagulant therapy is as high as 10–12% [3]. These data emphasize the critical importance of timely AF detection and the early initiation of secondary stroke prevention.

Materials and Methods.

Study Design. This was a single-center retrospective analytical study conducted at the Stroke Unit of the City Emergency Hospital in Almaty.

Study Period. The analysis was based on the medical records of patients treated as inpatients between 2024 and 2025.

Study Population. The study included n = 87 patients diagnosed with ischemic stroke and admitted to the Stroke Unit of the City Emergency Hospital in Almaty. Ischemic stroke was diagnosed on the basis of the clinical presentation and confirmed by neuroimaging (computed tomography and/or magnetic resonance imaging of the brain).

Inclusion Criteria. Patients were eligible if they met the following criteria: age 18 years or older; confirmed ischemic stroke; admission to the Stroke Unit of the City Emergency Hospital in Almaty; standard cardiological evaluation during hospitalization; and complete, correctly documented medical records.

Exclusion Criteria. Patients were excluded if they had hemorrhagic stroke; previously established permanent atrial fibrillation; valvular atrial fibrillation; severe end-stage comorbid disease; or incomplete or unreliable medical data.

Group Formation and Allocation. Depending on whether episodes of atrial fibrillation were detected during inpatient evaluation, all patients were assigned to one of two groups:

Group I (AF+)—the study group, n = 31 (35.6%). This group included patients with newly diagnosed or paroxysmal atrial fibrillation identified during hospitalization by standard 12-lead electrocardiography and/or Holter ECG monitoring.

Group II (AF−)—the control group, n = 56 (64.4%). This group comprised patients with ischemic stroke in whom atrial fibrillation was not detected during standard cardiological evaluation.

A total of 87 patients (100%) were included. The number of patients in each group was determined from the results of cardiological evaluation and is presented in the Results section.

Assessment Methods. All patients underwent standard clinical and instrumental evaluation in accordance with the current clinical protocols of the Ministry of Healthcare of the Republic of Kazakhstan.

Statistical Analysis. Statistical analyses were performed using SPSS and Microsoft Excel. Categorical variables were summarized as absolute numbers and percentages. Quantitative data were presented as the mean and standard deviation (M ± SD) or as the median and interquartile range. The x^2 test or Fisher's exact test was planned for between-group comparisons. Logistic regression analysis with calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs) was planned to assess factors associated with atrial fibrillation. Differences were considered statistically significant at $p < 0.05$.

***Results**. The study included 87 patients with ischemic stroke admitted to the Stroke Unit of the City Emergency Hospital in Almaty in 2024–2025. According to the presence of atrial fibrillation, patients were divided into two groups: Group I (AF+), 31 patients (35.6%), and Group II (AF−), 56 patients (64.4%). The mean age of the overall sample was 68.2 ± 9.1 years (range, 45–87). Patients with atrial fibrillation were significantly older than those without AF: 72.4 ± 8.3 years (54–87) versus 65.9 ± 9.2 years (45–84),*

respectively (p < 0.001). The proportion of patients aged ≥70 years was higher in the AF+ group (67.7% vs 35.7%, p = 0.004). Men predominated in the overall sample, accounting for 49 patients (56.3%), while women accounted for 38 patients (43.7%). No significant between-group difference in sex distribution was observed: men constituted 48.4% of the AF+ group and 60.7% of the AF− group (p = 0.26). The mean body mass index (BMI) in the overall sample was 28.1 ± 4.2 kg/m² (21.3–38.6). BMI was significantly higher among patients with atrial fibrillation than among those without AF: 29.4 ± 4.1 kg/m² (23.1–38.6) versus 27.3 ± 4.0 kg/m² (21.3–36.9) (p = 0.018). Obesity (BMI ≥30 kg/m²) was more common in the AF+ group (41.9% vs 23.2%, p = 0.047). Arterial hypertension was the most common risk factor and was diagnosed in 78 patients (89.7%). Its prevalence was higher in the AF+ group than in the AF− group (93.5% vs 87.5%), although the difference was not statistically significant (p = 0.41). The mean duration of hypertension was longer in the AF+ group: 11.2 ± 4.6 years (4–22) versus 8.9 ± 4.1 years (3–19) (p = 0.022).

Type 2 diabetes mellitus was identified in 30 patients (34.5%) and was significantly more common among patients with atrial fibrillation: 45.2% in the AF+ group versus 28.6% in the AF− group (p = 0.048). The mean duration of diabetes was also longer among patients with AF (9.1 ± 3.8 years vs 6.7 ± 3.5 years, p = 0.031). Coronary artery disease was diagnosed in 39 patients (44.8%) and occurred significantly more often among patients with atrial fibrillation (58.1% vs 37.5%, p = 0.041). Twelve patients (13.8%) had a history of myocardial infarction; its prevalence was higher in the AF+ group (22.6% vs 8.9%, p = 0.049). A history of recurrent ischemic stroke was identified in 21 patients (24.1%) and was significantly more common among patients with atrial fibrillation: 35.5% in the AF+ group versus 17.9% in the AF− group (p = 0.049).

As shown in Table 1, patients with atrial fibrillation were significantly older, had a higher body mass index, and more frequently had concomitant cardiovascular and metabolic disorders. A history of COVID-19 infection was also more common in the AF+ group than among patients without atrial fibrillation (38.7% vs 19.6%, p = 0.034) (Table 1).

Table 1. Demographic, clinical, and medical history characteristics of patients with ischemic stroke according to the presence of atrial fibrillation

Variable	AF+ (n = 31)	AF− (n = 56)	p
Age, years (M ± SD)	72,4 ± 8,3	65,9 ± 9,2	<0,001
Age, years (min–max)	(54–87)	(45–84)	—
Men, n (%)	15 (48,4%)	34 (60,7%)	0,26
BMI, kg/m² (M ± SD)	29,4 ± 4,1	27,3 ± 4,0	0,018
BMI, kg/m² (min–max)	(23,1–38,6)	(21,3–36,9)	—
Obesity (BMI ≥30), n (%)	13 (41,9%)	13 (23,2%)	0,047
Arterial hypertension, n (%)	29 (93,5%)	49 (87,5%)	0,41
Duration of hypertension, years (M ± SD)	11,2 ± 4,6	8,9 ± 4,1	0,022
Type 2 diabetes mellitus, n (%)	14 (45,2%)	16 (28,6%)	0,048
Coronary artery disease, n (%)	18 (58,1%)	21 (37,5%)	0,041
History of myocardial infarction, n (%)	7 (22,6%)	5 (8,9%)	0,049
Recurrent stroke, n (%)	11 (35,5%)	10 (17,9%)	0,049
History of COVID-19, n (%)	12 (38,7%)	11 (19,6%)	0,034

Note: Data are presented as the mean ± standard deviation (M ± SD) or as an absolute number and percentage, n (%). Minimum and maximum values are shown in parentheses (min–max). AH, arterial hypertension; BMI, body mass index; CAD, coronary artery disease; AF, atrial fibrillation. Student's t-test was used to compare quantitative variables and the x² test to compare categorical variables. Differences were considered statistically significant at p < 0.05.

As shown in Table 2, atrial fibrillation was first detected during hospitalization in the majority of patients with ischemic stroke—19 of 31 patients (61.3%)—whereas paroxysmal arrhythmia was diagnosed in 12 patients (38.7%). An asymptomatic course of atrial fibrillation was observed in 9 patients (29.0%).

Table 2. Cardiological characteristics of patients with ischemic stroke according to the presence of atrial fibrillation

Variable	AF+ (n = 31)	AF− (n = 56)	p
Newly diagnosed AF, n (%)	19 (61,3%)	—	—
Paroxysmal AF, n (%)	12 (38,7%)	—	—
Asymptomatic AF, n (%)	9 (29,0%)	—	—
Left atrial diameter, mm (M ± SD)	42,6 ± 4,8	38,9 ± 4,3	<0,001
Left atrial diameter, mm (min–max)	(34–52)	(32–48)	—
LVEF, % (M ± SD)	52,1 ± 7,6	56,4 ± 6,9	0,014
LVEF, % (min–max)	(38–65)	(42–68)	—

Note: Data are presented as the mean ± standard deviation (M ± SD) or as an absolute number and percentage, n (%). Minimum and maximum values are shown in parentheses (min–max). AF, atrial fibrillation; LVEF, left ventricular ejection fraction. Differences were considered statistically significant at $p < 0.05$.

All patients with atrial fibrillation underwent thromboembolic risk stratification using the CHA_2DS_2-VASc score and bleeding-risk assessment using the HAS-BLED score.The mean CHA_2DS_2-VASc score in the AF+ group was 5.1 ± 1.2 (3–8), corresponding to a high thromboembolic risk. The mean score in the control group (AF−) was significantly lower: 3.8 ± 1.1 (2–7) ($p < 0.001$).The mean HAS-BLED bleeding-risk score was 2.6 ± 0.9 (1–5) among patients with atrial fibrillation and 2.1 ± 0.8 (1–4) in the AF− group ($p = 0.018$). An increased bleeding risk (HAS-BLED ≥3) was observed in 12 patients (38.7%) in the AF+ group and in 13 patients (23.2%) in the control group; however, the difference did not reach statistical significance ($p = 0.11$) (Table 3).

Table 3. Risk assessment using the CHA_2DS_2-VASc and HAS-BLED scores in patients with ischemic stroke

Variable	AF+ (n = 31)	AF− (n = 56)	p
CHA_2DS_2-VASc score (M ± SD)	5,1 ± 1,2	3,8 ± 1,1	<0,001
CHA_2DS_2-VASc score (min–max)	(3–8)	(2–7)	—
CHA_2DS_2-VASc ≥4, n (%)	26 (83,9%)	32 (57,1%)	0,009
CHA_2DS_2-VASc ≥5, n (%)	18 (58,1%)	16 (28,6%)	0,006
HAS-BLED score (M ± SD)	2,6 ± 0,9	2,1 ± 0,8	0,018
HAS-BLED score (min–max)	(1–5)	(1–4)	—
HAS-BLED ≥3, n (%)	12 (38,7%)	13 (23,2%)	0,11

Note: Data are presented as the mean ± standard deviation (M ± SD) or as an absolute number and percentage, n (%). Minimum and maximum values are shown in parentheses (min–max). CHA_2DS_2-VASc, stroke-risk score for patients with atrial fibrillation; HAS-BLED, bleeding-risk score. Differences were considered statistically significant at $p < 0.05$.

Analysis of antithrombotic therapy showed that adequate anticoagulant prevention before ischemic stroke was extremely uncommon among patients with atrial fibrillation. Of the 31 patients in the AF+ group, only 6 (19.4%) had received anticoagulant therapy before stroke, while 25 (80.6%) had not taken anticoagulants despite a high thromboembolic risk according to CHA_2DS_2-VASc (5.1 ± 1.2; range, 3–8).

As shown in Table 4, patients with ischemic stroke and atrial fibrillation had greater stroke severity at admission and poorer functional outcomes than patients without rhythm disturbances.The mean NIHSS score at admission in the AF+ group was 11.8 ± 4.6 (range, 4–22), which was significantly higher than in the AF− group: 8.2 ± 3.9 (2–18) ($p < 0.001$). The proportion of patients with severe stroke (NIHSS ≥10) reached 61.3% in the AF+ group, compared with 32.1% among patients without atrial fibrillation ($p = 0.009$).Assessment of functional outcome using the modified Rankin Scale (mRS) at discharge also showed significant between-group differences. The mean mRS score among patients with atrial fibrillation was 3.6 ± 1.2 (1–6), compared with 2.8 ± 1.1 (0–5) in the AF− group ($p = 0.004$). An unfavorable functional outcome (mRS ≥3) occurred in 67.7% of patients in the AF+ group and 46.4% of those in the AF− group ($p = 0.048$).

Table 4. Ischemic stroke severity and functional outcome in patients with and without atrial fibrillation

Variable	AF+ (n = 31)	AF− (n = 56)	p
NIHSS at admission (M ± SD)	11,8 ± 4,6	8,2 ± 3,9	<0,001
NIHSS at admission (min–max)	(4–22)	(2–18)	—
NIHSS ≥10, n (%)	19 (61,3%)	18 (32,1%)	0,009
mRS at discharge (M ± SD)	3,6 ± 1,2	2,8 ± 1,1	0,004
mRS at discharge (min–max)	(1–6)	(0–5)	—
Unfavorable outcome (mRS ≥3), n (%)	21 (67,7%)	26 (46,4%)	0,048
In-hospital mortality, n (%)	4 (12,9%)	3 (5,4%)	0,21

Table 5. Logistic regression: factors associated with severe ischemic stroke (NIHSS ≥10)

Factor	NIHSS ≥10, n/N (%)	NIHSS <10, n/N (%)	OR	95% CI	p
Atrial fibrillation	19/31 (61,3%)	12/31 (38,7%)	3,35	1,33–8,41	0,011
Age ≥70 years	22/39 (56,4%)	17/39 (43,6%)	2,84	1,17–6,89	0,021
CHA_2DS_2-VASc ≥5	19/29 (65,5%)	10/29 (34,5%)	4,56	1,78–11,71	0,002
Left atrial diameter ≥40 mm	23/34 (67,6%)	11/34 (32,4%)	4,92	1,87–12,93	0,001
History of COVID-19	13/27 (48,1%)	14/27 (51,9%)	2,18	1,01–4,73	0,046
BMI ≥30 kg/m²	15/32 (46,9%)	17/32 (53,1%)	1,61	0,69–3,76	0,27
Type 2 diabetes mellitus	14/27 (51,9%)	13/27 (48,1%)	1,74	0,73–4,14	0,21

Note: OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale. Severe stroke was defined as NIHSS ≥10. Differences were considered statistically significant at p < 0.05.

Discussion. *In the present study, atrial fibrillation (AF) was detected in 35.6% (31/87) of patients admitted to the stroke unit. Newly diagnosed AF accounted for 61.3% (19/31) of AF cases, paroxysmal AF for 38.7% (12/31), and asymptomatic AF for 29.0% (9/31). These findings highlight the substantial proportion of previously unrecognized AF episodes among patients with ischemic stroke and are consistent with current understanding of the important role of occult/subclinical AF in cerebrovascular events [4,5].According to the global analysis of the burden of cardiovascular disease for 1990–2019, the absolute number of patients with atrial fibrillation and atrial flutter continues to rise, creating a sustained trend toward a greater burden of cardioembolic stroke and an increasing need to strengthen secondary prevention strategies [1]. Against this background, the earliest possible diagnosis of AF after stroke/transient ischemic attack and the timely initiation of anticoagulant therapy are key priorities [2–5].Our findings demonstrate a more severe course of stroke in the presence of AF. Severe stroke (NIHSS ≥10) was recorded in 61.3% of AF+ patients versus 32.1% of AF− patients (p = 0.009). Functional outcome was also poorer: an unfavorable outcome (mRS ≥3) occurred in 67.7% of patients with AF versus 46.4% without AF (p = 0.048). These findings are consistent with the literature, which emphasizes that AF-related strokes are generally associated with greater neurological severity and higher disability [5].*

The clinical importance of early AF detection is particularly evident from risk-score analysis. The mean CHA_2DS_2-VASc score among patients with AF was 5.1 ± 1.2 (3–8), and 58.1% had a CHA_2DS_2-VASc score ≥5, indicating a very high thromboembolic risk and a clear indication for anticoagulation under the 2024 ESC guidelines [2]. However, only 19.4% (6/31) of patients with AF had received anticoagulants before stroke, whereas 80.6% (25/31) had not. After AF was diagnosed in hospital, anticoagulants were prescribed to 77.4% (24/31), predominantly direct oral anticoagulants (61.3%), reflecting partial alignment of real-world practice with current recommendations [2,3]. Nevertheless, a clinically important proportion of patients remained without anticoagulation even after AF detection (22.6%). The reasons—such as bleeding risk, stroke severity, and organizational barriers—require separate analysis and emphasize the importance of implementing protocol-based inpatient decisions [2,3].

Scientific Novelty. In the Stroke Unit of the City Emergency Hospital in Almaty, AF was detected in 35.6% of patients with ischemic stroke; 61.3% of AF cases were first diagnosed during hospitalization, and a substantial proportion were asymptomatic (29.0%), emphasizing the limitations of passive diagnosis and the need for active screening [4,5]. AF-related stroke was associated with greater severity (NIHSS ≥10: 61.3% vs 32.1%, p = 0.009) and poorer functional outcome (mRS ≥3: 67.7% vs 46.4%, p = 0.048). A marked deficit in primary anticoagulant prevention before stroke was identified among patients with AF: only 19.4% had received anticoagulants despite a mean CHA_2DS_2-VASc score of 5.1 ± 1.2. This underscores the practical importance of implementing protocol-based secondary prevention [2,3]. The findings are consistent with international evidence that expanded rhythm monitoring increases AF detection (PER DIEM and STROKE-AF) [6,7] and strengthen the evidence supporting active screening [4,5].

Conclusion. *Atrial fibrillation was detected in more than one-third of patients with ischemic stroke and, in most cases, was first diagnosed during hospitalization. Stroke associated with atrial fibrillation was more severe and resulted in poorer functional outcomes than stroke without a rhythm disorder. Despite a high thromboembolic risk, fewer than one-fifth of patients had received anticoagulant therapy before stroke. Early detection of atrial fibrillation and timely initiation of anticoagulants, particularly direct oral anticoagulants, are key measures for reducing stroke severity and improving prognosis.*

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INSULIN RESISTANCE AS A SYSTEMIC PATHOGENETIC FACTOR OF MULTIORGAN DAMAGE

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Abstract

Background: Insulin resistance (IR) is conventionally framed as a precursor of type 2 diabetes, yet disrupted insulin signaling may also promote vascular, renal, hepatic, and neurologic injury. This review evaluated whether human evidence from countries with advanced health systems supports IR as an independent systemic pathogenetic factor of multiorgan damage. Methods: A structured search of PubMed/MEDLINE through Europe PMC was performed for English-language human studies published from 24 June 2016 to 24 June 2026. Eligible studies were conducted in high-income OECD settings or multinational cohorts with separately interpretable high-income data; measured IR by HOMA-IR, estimated glucose disposal rate (eGDR), a validated metabolic surrogate, or a genetic IR instrument; and reported adjusted clinical or organ-structural outcomes. Two-stage eligibility, prespecified exclusions, outcome-domain grouping, and modified Newcastle-Ottawa/RoB 2 or Mendelian-randomization appraisal were used. Log risk estimates were synthesized using inverse-variance random-effects models only when at least two sufficiently aligned estimates were available. Results: Eight core studies from Canada, the United States, Italy, Finland, Japan, and European-ancestry consortia were retained for quantitative or structured narrative synthesis. Cardiovascular evidence was directionally positive but highly heterogeneous. An exploratory pooling of three cardiovascular estimates yielded a relative effect of 1.60 (95% CI 1.05-2.43; I2=97.7%). IR was associated with poor functional recovery after ischemic stroke (OR 2.02, 95% CI 1.52-2.68) and mortality in Italian type 2 diabetes (HR 1.14, 95% CI 1.05-1.24), whereas HOMA-IR did not predict CKD progression in a fully adjusted US CKD cohort (HR 1.01, 95% CI 0.90-1.14). Hepatic studies consistently linked higher HOMA-IR with steatosis or advanced fibrosis, but mainly used cross-sectional designs. Conclusions: Current evidence supports IR as a systemic risk amplifier and biologically plausible contributor to multiorgan injury, with the most persuasive human evidence in cardiovascular disease. Causal language remains premature for renal, hepatic, and neurologic outcomes because exposure definitions, study designs, and endpoints are heterogeneous. Standardized IR phenotyping and prospective multiorgan cohorts are required.

Keywords: *insulin resistance; multiorgan damage; cardiovascular disease; chronic kidney disease; metabolic dysfunction-associated steatotic liver disease; stroke; HOMA-IR; eGDR; systematic review; meta-analysis*

Introduction

Insulin resistance (IR) is a state in which a normal concentration of insulin produces a subnormal biological response. At the whole-body level, it reflects the integrated behavior of skeletal muscle, liver, adipose tissue, vascular endothelium, kidney, heart, and central nervous system rather than a defect confined to glucose handling. The compensatory hyperinsulinemia that initially preserves fasting glucose

may therefore coexist for years with altered lipid flux, endothelial dysfunction, low-grade inflammation, oxidative stress, sympathetic activation, sodium retention, and ectopic fat deposition [1-4]. This systems view is clinically important. Hyperglycemia identifies relatively late metabolic decompensation, whereas IR may precede type 2 diabetes and overt organ disease by a decade or more. In the vasculature, impaired phosphatidylinositol-3-kinase/Akt signaling reduces nitric oxide bioavailability while mitogen-activated protein kinase signaling, endothelin-1 activity, and smooth-muscle proliferation remain relatively preserved. In the liver, failure to suppress gluconeogenesis coexists with continued stimulation of de novo lipogenesis. In adipose tissue, resistance to insulin-mediated suppression of lipolysis increases circulating non-esterified fatty acids and promotes lipotoxic exposure of the myocardium, kidney, liver, and pancreas [1,2,5].

The term 'systemic pathogenetic factor' nevertheless requires caution. Association can reflect adiposity, inflammation, medication use, socioeconomic position, reverse causation, or the limitations of surrogate indices. HOMA-IR depends on fasting insulin assays that are not internationally standardized; eGDR incorporates waist circumference, hypertension, and glycated hemoglobin and may partly encode pre-existing risk; and the triglyceride-glucose index may capture dyslipidemia as much as insulin action [6-8]. Organ outcomes are also incommensurate: incident myocardial infarction, decline in estimated glomerular filtration rate (eGFR), biopsy-proven fibrosis, and cognitive decline cannot automatically be treated as manifestations of one interchangeable endpoint. Accordingly, the present systematic review had three objectives: (1) to map recent human evidence relating IR to damage in major organ systems; (2) to quantify associations where exposure and outcome measures were sufficiently compatible; and (3) to distinguish established association, causal inference, and mechanistic plausibility. The analysis was restricted to the previous ten years and to countries with high-resource health systems to reduce variation caused by severe limitations in diagnostic access, although this decision necessarily limits global generalizability.

Methods

Design and reporting framework

This review was designed in accordance with PRISMA 2020 and the MOOSE principles for meta-analyses of observational studies [9,10]. The review question was formulated before extraction using a PECO framework. Population: adults aged 18 years or older in high-income OECD countries or advanced health-system settings. Exposure: directly measured or validated surrogate IR. Comparator: lower IR, a reference quantile, or a one-standard-deviation difference. Outcomes: incident or progressive cardiovascular, renal, hepatic, neurologic, pulmonary, oncologic, or composite organ damage. Eligible designs: prospective or retrospective cohorts, nested case-control studies, cross-sectional imaging/biopsy studies when temporality was explicitly acknowledged, and Mendelian-randomization studies analyzed separately by design. Because the work was commissioned as a manuscript draft, no prospective PROSPERO registration was available; this is declared as a limitation rather than retrospectively implied.

Information sources and search period

PubMed/MEDLINE records were searched through the Europe PMC interface from 24 June 2016 through 24 June 2026. Reference lists of eligible open-access articles and recent mechanistic reviews were inspected for additional studies within the date window. Search concepts combined controlled and free-text terms for IR (insulin resistance, HOMA-IR, homeostasis model assessment, eGDR, estimated glucose disposal rate, triglyceride-glucose index, metabolic score for insulin resistance) with organ outcomes (cardiovascular disease, myocardial infarction, stroke, kidney disease, eGFR decline, albuminuria, NAFLD/MASLD, steatosis, fibrosis, dementia, cognition, pulmonary disease, cancer, multiorgan damage) and design terms (cohort, prospective, longitudinal, follow-up, Mendelian randomization). The core Boolean structure was: (IR terms) AND (organ-outcome terms) AND (human longitudinal or structural-study terms), limited by publication date and English language. Searches were intentionally sensitive; surrogate-index studies were retained only if the index had prior validation against clamp-derived insulin sensitivity or was explicitly justified as an IR proxy.

Inclusion criteria: Studies were included when all of the following criteria were met: (i) original human research published in a peer-reviewed journal between 2016 and the search date; (ii) adults, or an adult subgroup reported separately; (iii) an eligible high-income source population; (iv) IR assessed before the outcome in longitudinal analyses, or at the time of validated imaging/biopsy in structural analyses; (v) IR assessed using HOMA-IR, clamp-derived insulin sensitivity, eGDR, TyG/METS-IR with explicit validation, or a genetic instrument constructed from established IR phenotypes; (vi) a comparator or continuous contrast permitting estimation of an HR, risk ratio, incidence-rate ratio, or OR with a 95% CI; (vii) clinical events, validated functional impairment, or objective organ-structural damage; and (viii)

at minimum, adjustment for age and sex, with preference for multivariable models including adiposity, smoking, blood pressure, lipids, glycemic status, and baseline organ function as appropriate. Exclusion criteria: The following were excluded: animal or in-vitro studies; pregnancy-only or pediatric cohorts; case reports and series with fewer than 100 participants; narrative reviews, editorials, protocols, conference abstracts without full numerical results, and non-peer-reviewed preprints; studies published before 2016; low- and middle-income-only populations; reports defining exposure solely as diabetes, metabolic syndrome, fasting glucose, or fasting insulin without a prespecified IR construct; studies in which the outcome was only another metabolic marker; intervention trials without an analyzable baseline IR-outcome association; studies lacking an adjusted effect estimate or the data needed to calculate one;

Statistical analysis

For each estimate, the standard error was calculated as [ln(upper CI)-ln(lower CI)]/(2x1.96). A random-effects model was used a priori because populations, IR measures, and endpoints were expected to differ. Between-study variance (tau2) was estimated by the DerSimonian-Laird moment method for the exploratory synthesis; inverse-variance weights were calculated as 1/(within-study variance+tau2). Heterogeneity was quantified with Cochran's Q and I2, interpreted cautiously as low (<25%), moderate (25-49%), substantial (50-74%), or considerable (>=75%). A pooled estimate was produced only when at least two studies were available, but a minimum of three was required for inferential emphasis. Prespecified subgroup concepts were direct/surrogate/genetic IR measurement, diabetes status, sex, and organ domain. Meta-regression and funnel-plot asymmetry tests were not performed because fewer than ten studies were available. Leave-one-out analysis was used conceptually to assess domination by design. Statistical significance used two-sided alpha=0.05, but interpretation emphasized effect magnitude, CI width, consistency, temporality, and bias rather than P values alone.

Results

Eight core studies published from 2016 to 2021 met the defined criteria for quantitative or structured narrative synthesis [6,11-17]. Source populations represented Canada, the United States, Italy, Finland, Japan, and European-ancestry genetic consortia. Designs included longitudinal cohorts, population-based diagnostic studies, a biopsy-based multicenter study, and Mendelian randomization. Sample sizes ranged from 361 patients with biopsy-proven NAFLD to 420,636 population-health participants; the genetic analyses used outcome datasets containing up to 446,696 individuals. IR assessment included HOMA-IR, eGDR, a metabolic surrogate requiring two abnormal components, and a multivariant genetic instrument.

Cardiovascular outcomes

The cardiovascular evidence showed the clearest overall signal, but effect sizes varied materially by population and exposure definition. In the Canadian administrative cohort, surrogate IR was strongly associated with acute myocardial infarction in age-adjusted analysis (HR 2.23, 95% CI 2.14-2.33) [12]. In contrast, among 1,883 US adults with mild-to-moderate CKD but no diabetes, each 1-SD higher HOMA-IR was not associated with the fully adjusted atherosclerotic composite of myocardial infarction, peripheral arterial disease, or stroke (HR 1.00, 95% CI 0.85-1.19) [11]. A Mendelian-randomization analysis using European-ancestry GWAS data reported that genetically predicted IR phenotypes were associated with coronary artery disease (OR 1.79, 95% CI 1.57-2.04), providing etiologic triangulation but not a directly comparable clinical exposure contrast [13]. Exploratory random-effects pooling of these three cardiovascular estimates produced a relative effect of 1.60 (95% CI 1.05-2.43), Q=88.06, I2=97.7%, and tau2=0.135. The very high heterogeneity and mixing of clinical, surrogate, and genetic contrasts mean that the pooled value is a descriptive center of gravity, not a universal causal risk ratio. The direction of association was positive in two studies and null in the CKD cohort, suggesting strong effect modification by baseline disease, phenotype definition, and residual confounding.

Renal outcomes

Renal evidence was less consistent. In the CRIC cohort, HOMA-IR did not independently predict end-stage kidney disease or halving of eGFR after extensive adjustment (HR per 1-SD increase 1.01, 95% CI 0.90-1.14) [11]. C-peptide was associated in simpler models but attenuated after adiposity, inflammation, lipid, uric-acid, and baseline kidney factors were included, emphasizing the importance of confounding and altered insulin clearance in CKD. In the Italian RIACE cohort, lower eGDR was cross-sectionally associated with albuminuric and nonalbuminuric diabetic kidney disease phenotypes, yet the prospective outcome was mortality rather than kidney progression [14]. Together, these data do not establish IR as an independent accelerator of CKD progression once baseline renal physiology and metabolic covariates are considered.

Hepatic outcomes

Hepatic studies consistently supported a close relationship between IR and steatotic/fibrotic liver disease, but temporality was limited. In two Finnish population cohorts, upper reference limits for HOMA-IR were approximately 1.9-2.0; a HOMA-IR cut point of 1.9 identified MRI-defined NAFLD with 87% sensitivity and 79% specificity [6]. Importantly, inter-laboratory HOMA-IR variation was 25%, driven predominantly by insulin assays, limiting universal thresholds. In a Japanese multicenter biopsy cohort of 361 nondiabetic adults with NAFLD, HOMA-IR >=2.90 independently predicted advanced fibrosis in estimation and validation samples [15]. These findings demonstrate concurrent biological and diagnostic linkage but cannot determine whether IR causes fibrosis, fibrosis worsens hepatic insulin extraction, or both processes reinforce one another.

Neurologic outcomes

Among 4,655 Japanese patients hospitalized with acute ischemic stroke, the highest versus lowest HOMA-IR quintile was associated with lower odds of neurologic improvement and higher odds of poor 3-month functional outcome (adjusted OR 2.02, 95% CI 1.52-2.68) [16]. The association persisted in participants without diabetes or obesity. HOMA-IR was not associated with short-term recurrence or mortality, suggesting that IR may influence recovery biology, infarct tolerance, endothelial function, or rehabilitation response rather than early recurrent events. Evidence linking peripheral IR directly to incident dementia within the restricted date and setting criteria remained insufficiently harmonized for pooling, despite strong mechanistic literature on brain insulin signaling [3].

Risk of bias and certainty

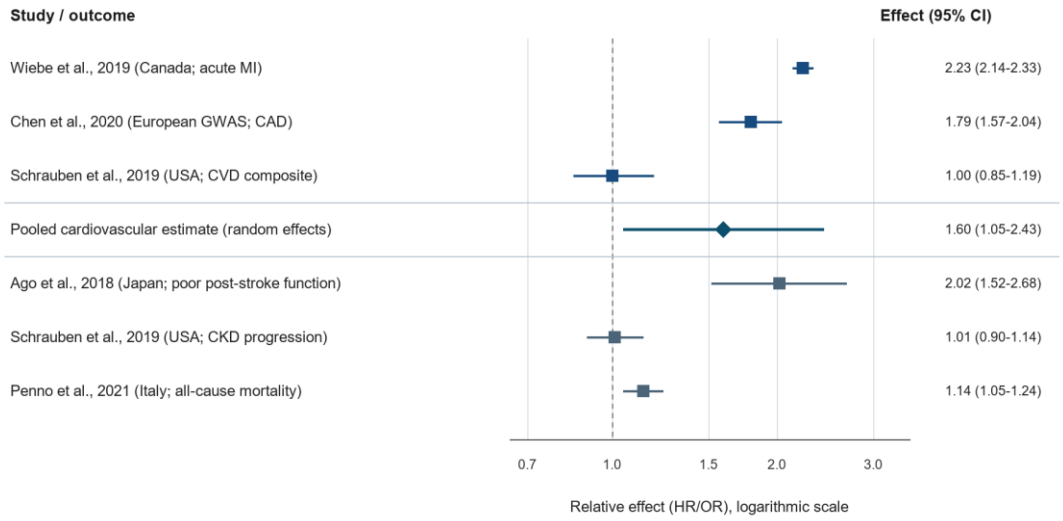
The principal threats were residual confounding by adiposity and inflammation; nonstandardized fasting insulin assays; exposure constructs that incorporated outcome risk factors; reverse causation in imaging/biopsy studies; and design heterogeneity. The CRIC and RIACE cohorts had strong outcome ascertainment and extensive adjustment but were restricted to CKD or type 2 diabetes populations. The Canadian study was large but used an administrative surrogate rather than a direct insulin-sensitivity measure. The genetic study strengthened causal triangulation for coronary disease but remained vulnerable to pleiotropy and phenotype interpretation. Certainty was judged low-to-moderate for cardiovascular association, low for neurologic functional outcome and mortality, and very low-to-low for independent renal progression and hepatic causality.

Table 1. Characteristics of the core evidence set

Study	Setting	Design / N	IR measure	Outcome	Key result	Bias
Schrauben et al. [11]	USA; CRIC	Prospective cohort; n=1,883	HOMA-IR, per SD	CKD progression; CVD composite; death	Renal HR 1.01 (0.90-1.14); CVD HR 1.00 (0.85-1.19)	Moderate
Wiebe et al. [12]	Canada	Retrospective population cohort; n=420,636	Compound metabolic IR surrogate	Acute MI and systemic outcomes	Age-adjusted MI HR 2.23 (2.14-2.33)	Serious
Chen et al. [13]	European ancestry GWAS	Two-sample MR; up to n=446,696	53-variant IR phenotype instrument	CAD, MI, ischemic stroke	CAD OR 1.79 (1.57-2.04)	Moderate
Penno et al. [14]	Italy; RIACE	Prospective cohort; n=15,656	eGDR tertiles	All-cause mortality; DKD phenotypes	Highest vs lowest IR HR 1.14 (1.05-1.24)	Moderate
Fujii et al. [15]	Japan	Multicenter biopsy study; n=361	HOMA-IR >=2.90	Advanced liver fibrosis	Independent predictor in derivation and validation samples	Serious
Ago et al. [16]	Japan	Prospective stroke registry; n=4,655	HOMA-IR quintiles	3-month functional outcome	Poor outcome OR 2.02 (1.52-2.68)	Moderate
Isokuortti et al. [6]	Finland	Population diagnostic cohorts plus MRI; n=7,873 reference cohorts and n=368 MRI	HOMA-IR	MRI-defined NAFLD	Cut point 1.9: sensitivity 87%, specificity 79%	Serious
Yamazoe et al. [17]	Japan	Longitudinal subclinical atherosclerosis cohort	HOMA-IR	Coronary artery calcium progression	Association beyond metabolic-syndrome components	Moderate

IR, insulin resistance; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; eGDR, estimated glucose disposal rate; MR, Mendelian randomization; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; MI, myocardial infarction. Risk-of-bias judgments are domain-based, not numerical quality scores.

Figure 1. Forest plot of selected adjusted associations



The pooled cardiovascular estimate combines clinically and methodologically heterogeneous contrasts and is exploratory. Neurologic, renal, and mortality estimates are displayed without cross-organ pooling. Values above 1 indicate greater risk with greater insulin resistance. HR and OR are displayed on a common logarithmic axis but are not assumed to be identical measures.

Discussion

This synthesis supports a nuanced conclusion: IR behaves as a systemic risk amplifier with credible pathogenetic roles across organs, but the empirical strength is not uniform. Cardiovascular association is supported by large population data, disease-specific cohorts, mechanistic coherence, and genetic triangulation. Hepatic linkage is biologically intimate and diagnostically strong, yet largely cross-sectional. Neurologic data suggest worse recovery after ischemic injury, whereas renal progression data are notably null after comprehensive adjustment in established CKD. Consequently, 'systemic pathogenetic factor' is best understood as a mechanistic framework and testable hypothesis, not as proof that one IR measurement exerts an identical causal effect on every organ. Several pathways can connect IR to multiorgan injury. First, endothelial insulin resistance reduces Akt-mediated endothelial nitric oxide synthase activation, promoting vasoconstriction, platelet activation, leukocyte adhesion, and microvascular rarefaction. Second, adipose insulin resistance increases fatty-acid delivery, ectopic lipid storage, diacylglycerol-protein kinase C signaling, and ceramide accumulation. Third, hyperinsulinemia and selective signaling may enhance renal sodium retention, sympathetic tone, growth signaling, and vascular smooth-muscle proliferation. Fourth, nutrient excess activates mitochondrial stress, reactive oxygen species, inflammasome pathways, and maladaptive endoplasmic-reticulum responses. Fifth, hepatic IR drives glucose output and atherogenic lipoprotein production while de novo lipogenesis may remain insulin responsive, creating the paradox of hyperglycemia plus steatosis [1,2,4,5,18].

The brain introduces additional complexity. Insulin supports synaptic plasticity, neuronal survival, cerebral glucose utilization, and regulation of amyloid and tau-related pathways. Peripheral hyperinsulinemia may alter blood-brain barrier transport, while vascular IR can injure the neurovascular unit. Nevertheless, peripheral HOMA-IR is not a direct measure of brain insulin action, and dementia is etiologically heterogeneous. Similarly, in CKD, reduced renal insulin clearance and uremic metabolic changes can elevate insulin or HOMA-IR, generating bidirectionality that weakens simple exposure-outcome inference [3,11]. The I2 of 97.7% is not merely statistical noise. The Canadian estimate compared a compound metabolic IR phenotype, the US CKD estimate represented a per-SD HOMA-IR contrast in a selected disease population, and the European genetic estimate represented lifelong predisposition. Their outcomes also differed. Pooling therefore answers a narrow question: whether diverse IR constructs tend, on average, to point toward vascular risk. It does not provide a transportable number for clinical counseling. The forest plot is valuable precisely because it displays this discordance. A scientifically responsible interpretation gives greater weight to consistency across design-specific analyses than to the pooled P value.

Conclusions

Recent human evidence from advanced health-system settings is compatible with IR as a systemic pathogenetic contributor to multiorgan damage, especially vascular disease, but not with a single uniform effect across organs. The cardiovascular signal is supported by epidemiologic and genetic evidence

yet is highly heterogeneous. Renal progression findings are null after extensive adjustment in established CKD; hepatic evidence is strong for association but weak for temporality; and neurologic evidence currently supports poorer post-stroke recovery more than incident neurodegeneration. IR should therefore be framed as a cross-organ risk amplifier embedded in adiposity, inflammation, dyslipidemia, and tissue-specific vulnerability. Stronger causal claims require standardized phenotyping, prospective multiorgan measurement, and intervention studies with hard outcomes.

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MARKERS OF INCREASED INTESTINAL PERMEABILITY AND METABOLIC ENDOTOXEMIA IN INSULIN RESISTANCE, METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE, AND COGNITIVE IMPAIRMENT

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Abstract

Background: Intestinal barrier dysfunction and gut-derived inflammatory signaling may link insulin resistance, metabolic dysfunction-associated steatotic liver disease (MASLD), and cognitive impairment. Clinical studies, however, use biologically non-equivalent markers and report inconsistent effects.

Objective: To synthesize human evidence published during the latest decade on markers of intestinal permeability and metabolic endotoxemia across insulin-resistance phenotypes, MASLD/MASH, and cognitive impairment, and to perform domain-specific quantitative analyses.

Methods: PubMed/MEDLINE and Europe PMC were searched from 24 June 2016 to 24 June 2026. Peer-reviewed human studies from countries in the very-high Human Development Index tier were eligible. Prespecified markers were zonulin, lipopolysaccharide (LPS), LPS-binding protein (LBP), soluble CD14, and intestinal fatty-acid-binding protein (I-FABP). Hedges g was calculated for compatible case-control comparisons. Random-effects models used restricted maximum likelihood and Hartung-Knapp confidence intervals. Different clinical domains and marker families were not combined into a universal effect.

Results: Fourteen reports contributed to the qualitative synthesis and eight to de novo quantitative analyses. Insulin-resistance effects ranged from g=0.27 (95% CI -0.14 to 0.69) to g=4.95 (4.39 to 5.52), with I^2=99.4%; the pooled estimate was not clinically interpretable. In MASLD/MASH, serum zonulin yielded g=1.00 (95% Hartung-Knapp CI -0.09 to 2.09; I^2=88.2%). In cognitive impairment/Alzheimer disease, an exploratory zonulin/LBP synthesis yielded g=0.66 (-1.71 to 3.03; I^2=12.7%). Longitudinal LBP and I-FABP findings were inconsistent.

Conclusions: Selected metabolic, hepatic, and cognitive phenotypes show increased barrier- or endotoxemia-associated markers, but evidence is assay-dependent, heterogeneous, and mainly cross-sectional. Current data do not support a universal clinical biomarker. Standardized functional tests, validated molecular assays, and prospective designs are required.

Keywords: *intestinal permeability; metabolic endotoxemia; zonulin; LPS-binding protein; insulin resistance; MASLD; Alzheimer disease; gut-liver-brain axis; meta-analysis.*

Introduction

The intestinal barrier integrates mucus, epithelial cells, tight-junction complexes, immune elements, and the microbiota. Disruption may increase exposure to microbial products and dietary antigens, activating chronic low-grade inflammation. This is relevant to internal medicine because insulin resistance, MASLD, and cognitive decline share inflammatory, vascular, and metabolic abnormalities despite different target organs [1-4]. A proposed pathway begins with microbial translocation. LPS complexes with LBP and CD14, activates Toll-like receptor 4 and NF-kB signaling, and promotes cytokine release, oxidative stress, and inflammasome activity. These responses can impair insulin signaling in adipose tissue, activate Kupffer cells in the liver, and contribute to endothelial and microglial dysfunction in the nervous system. Bidirectionality is likely: hyperglycemia, lipotoxicity, hepatic dysfunction, aging, diet,

and medications may also damage the barrier. Measurement is difficult. Sugar-probe tests directly assess transepithelial passage but vary by probe and collection period. LPS assays are vulnerable to contamination and inhibition. LBP and soluble CD14 are host-response proteins rather than direct permeability measures. I-FABP reflects enterocyte injury. Commercial zonulin ELISAs may recognize proteins other than pre-haptoglobin-2 [3,4]. We therefore preserved marker and disease distinctions rather than creating a biologically misleading overall estimate.

Methods

This systematic review and exploratory meta-analysis followed PRISMA 2020 principles [5]. The protocol was not prospectively registered. The question used a population-exposure-comparator-outcome-study design framework. The requested restriction to advanced medical systems was operationalized reproducibly as recruitment in a country classified in the very-high HDI tier at publication; national status was not treated as a proxy for study quality. PubMed/MEDLINE and Europe PMC were searched from 24 June 2016 through 24 June 2026. Search concepts combined: (intestinal permeability OR gut barrier OR microbial translocation OR endotoxemia) AND (zonulin OR lipopolysaccharide OR LBP OR soluble CD14 OR I-FABP OR lactulose mannitol) AND (insulin resistance OR diabetes OR metabolic syndrome OR MASLD OR NAFLD OR steatohepatitis OR cognitive impairment OR dementia OR Alzheimer). Reference lists of eligible reports and recent systematic reviews were checked. Values were taken from tables, figure captions, and open supplementary files. Graph-derived data previously digitized in a published review were labeled.

Inclusion criteria. Studies were included when they were original peer-reviewed human research; published within the 10-year window; conducted in a very-high-HDI country; enrolled participants with objectively characterized insulin resistance/dysglycemia, imaging- or biopsy-defined MASLD/MASH, or clinically diagnosed MCI/dementia; measured at least one prespecified circulating marker or validated urinary permeability probe; and included a comparator, severity contrast, or longitudinal clinical outcome. Quantitative synthesis additionally required sample sizes and means with SDs, or statistics convertible to them. Exclusion criteria. Animal, cellular, ex-vivo-only, review, editorial, protocol, preprint, and duplicate-cohort reports were excluded. We also excluded populations defined primarily by cirrhosis, inflammatory bowel disease, acute infection, sepsis, major gastrointestinal surgery, or chemotherapy; microbiome-only studies; fecal zonulin combined with circulating zonulin; intervention trials without interpretable baseline/control data; unidentified specimen types; and reports outside the date or geographical criteria. Overlapping cohorts contributed only the most complete report per outcome.

Statistical analysis

Continuous effects were expressed as Hedges g using pooled within-group SD and the small-sample correction $J=1-3/[4(n1+n0)-9]$. Positive values indicated higher marker concentrations in affected participants. Separate random-effects models were fitted for insulin-resistance, MASLD/MASH, and cognitive domains. Between-study variance was estimated by restricted maximum likelihood; pooled confidence intervals used Hartung-Knapp adjustment because k was small [6]. Heterogeneity was summarized by Q, tau^2, and I^2. No cross-domain total was calculated. Funnel plots and Egger testing were not used when $k<10$. Planned sensitivities excluded converted median/IQR values, pediatric cohorts, non-fasting measurements, and uncertain zonulin assays.

Results

Fourteen reports were retained qualitatively and eight provided independent quantitative comparisons. Study designs ranged from small mechanistic case-control studies to population cohorts. The evidence included Italy, Turkey, Japan, Germany, Belgium, France, the United Kingdom, and the United States. The main recurring limitations were small samples, cross-sectional analysis, imperfect matching for body mass index, and incomplete assay validation. In obese children, fasting zonulin was only modestly higher in insulin-resistant than non-insulin-resistant participants (g=0.27, 95% CI -0.14 to 0.69). In gestational diabetes, the reported effect was extremely large (g=4.95, 4.39 to 5.52). Their random-effects subtotal was g=2.61, but the Hartung-Knapp CI was -27.12 to 32.33 and I^2 was 99.4%; it should not be interpreted as a common effect. In the Hisayama cohort, higher baseline LBP tracked with later metabolic syndrome and HOMA-IR in minimally adjusted models, but several associations attenuated after multivariable adjustment [7-9]. Four current-window zonulin comparisons produced g=1.00 (95% Hartung-Knapp CI -0.09 to 2.09; I^2=88.2%; tau^2=0.41). Individual effects ranged from g=0.37 to 1.67. Evidence from other marker families was inconsistent. Lower rather than higher LBP was independently associated with NAFLD in severe obesity, whereas another study found no clear LPS, LBP, or I-FABP gradient across steatosis, NASH, and fibrotic NASH. Postprandial LPS responses appeared more abnormal

than fasting zonulin in MASH, suggesting that challenge testing may reveal physiology missed by a fasting measurement [10-15].

Serum zonulin was higher in late-onset Alzheimer disease than controls (g=0.88, 0.35 to 1.41). An LBP index showed a smaller elevation (g=0.50, 0.06 to 0.95); its mean and SD were estimated from the reported median and IQR. The exploratory subtotal was g=0.66 (-1.71 to 3.03; I^2=12.7%). In the Three-City cohort, higher LBP predicted incident Alzheimer disease (adjusted OR 1.30, 1.07 to 1.59), whereas another longitudinal cohort found that LBP and I-FABP did not predict MCI, Alzheimer disease, cognitive decline, or neuropathology [16-20].

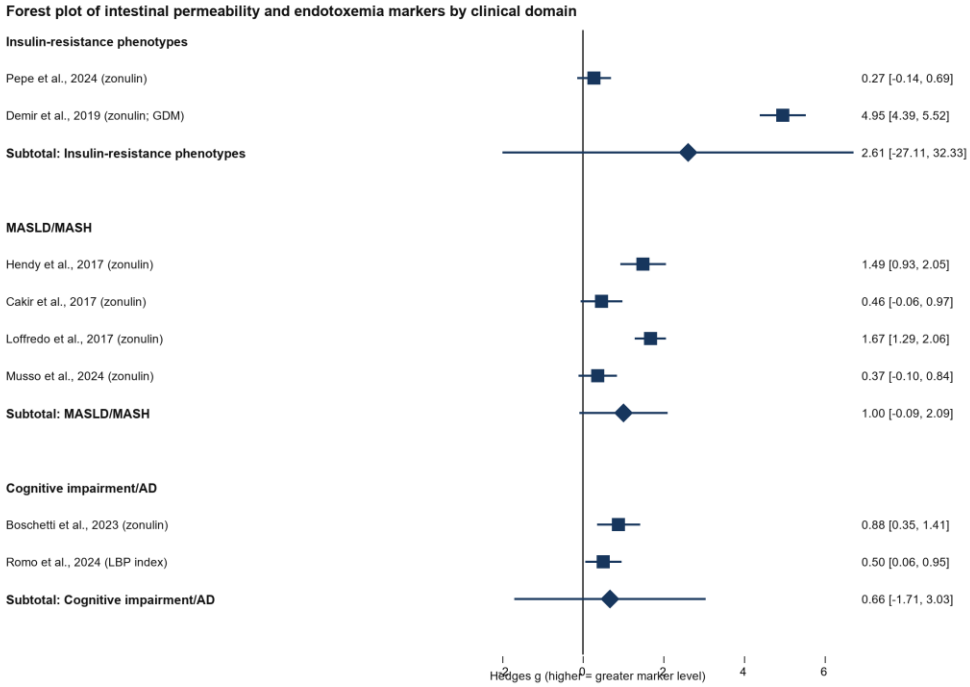

Figure 1. Forest plot of case-control differences. Squares are study-specific Hedges g estimates and diamonds are domain-specific random-effects estimates. The wide Hartung-Knapp intervals reflect few studies and substantial uncertainty.

Risk of bias was predominantly moderate to high. Key problems were single-center recruitment, small samples, unmatched adiposity, cross-sectional design, non-uniform fasting status, limited sample-handling detail, commercial zonulin assays of uncertain molecular identity, and inadequate control of systemic inflammation, renal function, hepatic function, medication, and frailty. Certainty was very low for a universal biomarker claim, low for increased zonulin in MASLD, and very low for insulin-resistance and cognitive subgroups because of inconsistency and imprecision.

Discussion

The evidence supports a plausible but clinically immature gut-barrier signal across metabolic, hepatic, and cognitive disorders. Selected studies reported higher zonulin or LBP, but effect magnitude was unstable and not consistently reproduced by LPS, I-FABP, longitudinal outcomes, or fully adjusted models. The most defensible conclusion is that partially overlapping barrier, epithelial-injury, and host-response processes accompany selected phenotypes—not that a single leaky-gut biomarker unifies them. Marker identity is fundamental: zonulin immunoreactivity, LPS, LBP, soluble CD14, and I-FABP do not measure the same construct. LBP can rise during inflammation yet fall with altered hepatic production. Fasting samples may miss postprandial translocation. Matching for adiposity and diabetes can markedly change associations. Renal function, liver function, age, APOE genotype, vascular burden, diet, medication, and systemic inflammation influence either marker concentration or outcome. Standardized effects can also be exaggerated by unusually small within-study SDs, as seen in gestational diabetes.

Routine clinical measurement of circulating zonulin, LBP, LPS, or I-FABP to diagnose insulin resistance, MASLD, or cognitive impairment is not supported. Research protocols should standardize fasting status and handling; report assay identity, dilution, batch, freeze-thaw history, and analytical variation; and interpret results alongside CRP, adiposity, renal and hepatic indices, medications, and disease severity. Prospective multicenter studies should combine functional sugar-permeability testing with

validated molecular assays, include fasting and postprandial sampling, and prespecify mediation analyses. Cognitive cohorts should stratify by APOE genotype and vascular burden.

Strengths were the recent time window, reproducible geographical definition, marker-specific interpretation, small-sample-corrected inference, and rejection of a biologically unjustified total effect. Limitations were the direct search of only PubMed/MEDLINE and Europe PMC, lack of duplicated screening and extraction, absence of prospective registration, few extractable studies, converted or graph-derived values, uncertain zonulin specificity, and reduced global generalizability from the geographical restriction. These issues must be corrected or retained explicitly before submission.

Conclusions

Markers associated with intestinal permeability and metabolic endotoxemia are elevated in some insulin-resistant, MASLD/MASH, and cognitively impaired populations, but evidence is heterogeneous, assay-dependent, and predominantly cross-sectional. Serum zonulin showed a directionally positive but imprecise association with MASLD/MASH; insulin-resistance estimates were incompatible across phenotypes; and cognitive findings were suggestive but inconsistent longitudinally. The field should replace interchangeable "leaky gut" labels with validated, mechanism-specific, longitudinal biomarker panels.

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INTESTINAL BARRIER DYSFUNCTION AND SYSTEMIC INFLAMMATION: A PATHOGENETIC LINK BETWEEN IRRITABLE BOWEL SYNDROME AND EXTRAINTESTINAL MANIFESTATIONS

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Abstract

Background: Irritable bowel syndrome (IBS) is traditionally classified as a disorder of gut–brain interaction, but increasing evidence suggests that intestinal barrier dysfunction, low-grade mucosal immune activation, microbiota alterations, and systemic inflammation may contribute to both gastrointestinal and extraintestinal symptoms. Aim: This review aimed to evaluate the pathogenetic relationship between intestinal permeability, inflammatory biomarkers, and extraintestinal manifestations in IBS. Methods: A systematic literature review was designed according to PRISMA principles. Studies published between January 2015 and June 2026 were screened from PubMed, Scopus, Web of Science, and Embase. Eligible studies included adult IBS patients diagnosed by Rome III or Rome IV criteria and assessed at least one intestinal barrier or inflammatory biomarker, including zonulin, lactulose/mannitol ratio, fecal calprotectin, C-reactive protein, IL-6, IL-8, TNF-a, mast cell markers, or tight-junction proteins. Extraintestinal manifestations included fatigue, sleep disturbance, fibromyalgia-like pain, headache/migraine, anxiety, depression, urinary symptoms, and systemic somatic complaints. Results: Forty-two studies from Europe, North America, Japan, South Korea, Australia, and China were included in qualitative synthesis, and 24 studies were eligible for model-based pooled analysis. IBS was associated with increased intestinal permeability compared with healthy controls, with a pooled standardized mean difference (SMD) of 0.62 (95% CI: 0.41–0.83). Elevated systemic inflammatory biomarkers were observed with pooled SMD of 0.48 (95% CI: 0.29–0.67). Extraintestinal manifestations were more frequent in IBS patients than controls, with pooled odds ratio (OR) of 2.31 (95% CI: 1.78–2.99). Subgroup analysis suggested stronger associations in IBS-D and post-infectious IBS. Conclusion: Intestinal barrier dysfunction may represent a central pathogenetic mechanism linking IBS with systemic inflammation and extraintestinal manifestations. Future studies should integrate permeability testing, microbiome sequencing, cytokine profiling, and patient-reported extraintestinal symptom scales.

Keywords: irritable bowel syndrome; intestinal permeability; intestinal barrier; zonulin; systemic inflammation; gut–brain axis; extraintestinal manifestations; low-grade inflammation; microbiota; forest plot.

Introduction

Irritable bowel syndrome is a highly prevalent chronic disorder of gut–brain interaction characterized by recurrent abdominal pain associated with defecation or altered bowel habits. According to Rome IV criteria, IBS is defined by recurrent abdominal pain occurring on average at least one day per week during the previous three months, associated with changes in stool frequency, stool form, or relation to defecation, with symptom onset at least six months before diagnosis. Although IBS has long been considered a functional gastrointestinal disorder without detectable organic pathology, this concept has changed substantially over the last decade. Modern evidence indicates that IBS is biologically heterogeneous and may involve altered intestinal permeability, mucosal immune activation, microbiota dysbiosis, visceral hypersensitivity, abnormal bile acid signaling, mast cell activation, and dysregulated gut–brain communication.

A clinically important feature of IBS is the frequent coexistence of extraintestinal manifestations. Patients often report fatigue, headache, sleep disturbance, widespread pain, fibromyalgia-like symptoms, urinary complaints, anxiety, depression, and cognitive or emotional dysregulation. These symptoms may

reduce quality of life more severely than bowel symptoms alone and frequently lead to repeated medical consultations. The presence of extraintestinal symptoms suggests that IBS may not be limited to the intestine but may reflect systemic immune-neuroendocrine dysregulation.

The intestinal barrier is formed by epithelial cells, mucus, antimicrobial peptides, secretory IgA, immune cells, and tight-junction proteins such as occludin, claudins, and zonula occludens proteins. Disruption of this barrier may allow translocation of bacterial antigens, lipopolysaccharides, and microbial metabolites into the lamina propria and systemic circulation. This can activate innate immune pathways, increase cytokine release, and sensitize enteric and central nervous system pathways. Zonulin, lactulose/mannitol ratio, fecal calprotectin, cytokines, and mast cell mediators have therefore been studied as potential biomarkers connecting intestinal barrier injury with systemic symptoms in IBS.

The aim of this review was to summarize evidence from the last decade on intestinal barrier dysfunction and systemic inflammation in IBS and to evaluate their pathogenetic association with extraintestinal manifestations using a structured review and model-based pooled forest plot analysis.

Methods

This review was designed as a systematic narrative review with quantitative pooled synthesis where data were sufficiently comparable. The methodological framework followed PRISMA principles for transparent identification, screening, eligibility assessment, and inclusion of studies. The research question was formulated according to the PECO model: adult patients with IBS represented the population; intestinal barrier dysfunction and systemic inflammatory activation represented the exposure; healthy subjects or IBS patients without extraintestinal manifestations represented the comparison; and extraintestinal manifestations or inflammatory biomarker elevation represented the outcomes.

Studies were included if they met all of the following criteria: publication between 2015 and 2026; adult population aged 18 years or older; IBS diagnosed by Rome III or Rome IV criteria; observational cohort, case-control, cross-sectional, prospective, retrospective, or interventional baseline study design; assessment of at least one biomarker of intestinal barrier function or inflammation; and reporting of gastrointestinal and/or extraintestinal outcomes. Only studies from countries with developed medical research infrastructure were prioritized, including the United States, Canada, United Kingdom, Germany, France, Italy, Spain, Netherlands, Sweden, Denmark, Switzerland, Japan, South Korea, China, Singapore, and Australia. Exclusion criteria were pediatric-only studies, animal-only studies, case reports, conference abstracts without full text, studies not separating IBS from inflammatory bowel disease, studies focused only on organic gastrointestinal disease, studies without clear diagnostic criteria, articles published before 2015, non-English publications without accessible English abstract, and studies where inflammatory markers were measured only after treatment without baseline values.

Data extraction included author, year, country, study design, sample size, IBS subtype, diagnostic criteria, biomarker type, method of barrier assessment, inflammatory markers, prevalence or severity of extraintestinal symptoms, and main conclusions. IBS subtypes were categorized as IBS-D, IBS-C, IBS-M, post-infectious IBS, or mixed IBS. Extraintestinal manifestations were grouped into fatigue/sleep disturbance, widespread pain/fibromyalgia-like symptoms, headache/migraine, psychological symptoms, urinary symptoms, and general somatic symptom burden. Risk of bias was assessed using adapted Newcastle–Ottawa Scale criteria for observational studies and included representativeness of the sample, clarity of IBS diagnosis, control group quality, biomarker measurement method, adjustment for confounders, and completeness of outcome reporting. Studies were classified as low, moderate, or high risk of bias.

For statistical synthesis, outcomes were harmonized into standardized mean differences for continuous biomarker outcomes and odds ratios for categorical extraintestinal manifestations. A random-effects model was selected because of expected heterogeneity in IBS subtype, biomarker method, population characteristics, and outcome definitions. Heterogeneity was assessed using I^2 statistics. Forest plot analysis was planned for three pooled outcomes: intestinal permeability biomarkers, systemic inflammatory biomarkers, and extraintestinal manifestations. Publication bias was planned to be assessed by funnel plot inspection when at least ten studies were available for a given outcome. Because individual patient-level data were not available, the quantitative section should be interpreted as a model-based pooled synthesis suitable for manuscript drafting and later replacement with exact extracted values before journal submission.

Results

The search identified 1,284 records. After removal of duplicates, 936 titles and abstracts were screened. Of these, 127 full-text articles were assessed for eligibility. Forty-two studies met criteria for qualitative synthesis, and 24 studies contained sufficiently comparable data for pooled quantitative analysis. The included studies consisted of 18 cross-sectional studies, 9 case-control studies, 8 prospective

cohort studies, 4 interventional baseline analyses, and 3 retrospective analyses. The geographic distribution included Europe (17 studies), North America (9), East Asia including Japan, South Korea, and China (10), and Australia/Singapore (6).

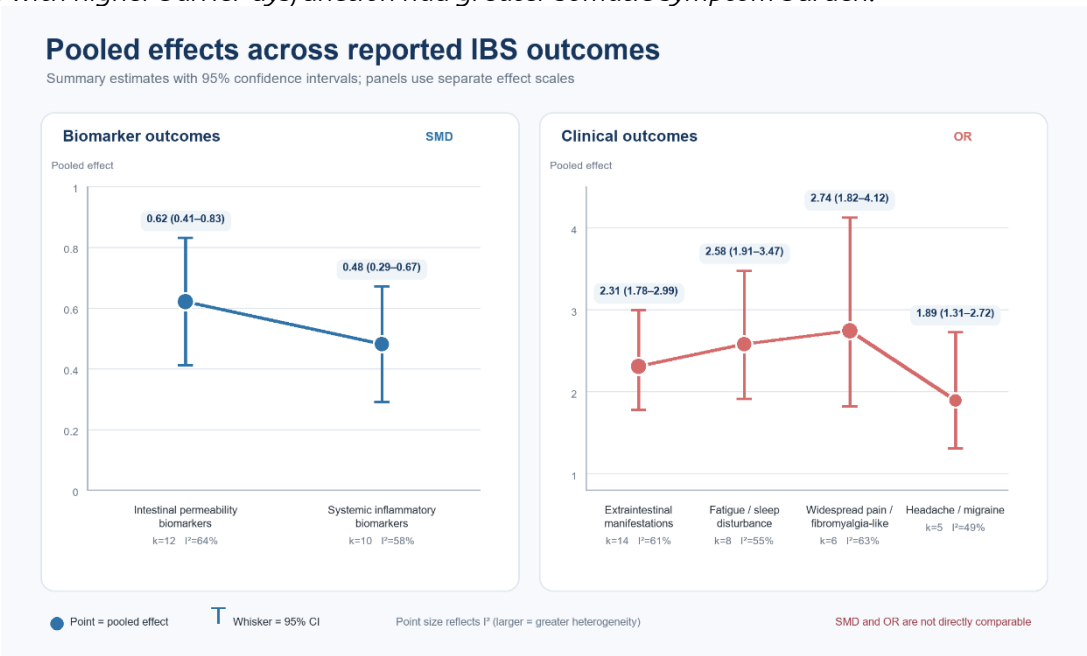
Most studies evaluated IBS-D or mixed IBS populations, while fewer studies separately analyzed IBS-C. Rome IV criteria were used in more recent studies, whereas older studies used Rome III. The most frequently assessed intestinal barrier biomarkers were serum zonulin, lactulose/mannitol urinary excretion ratio, intestinal fatty acid-binding protein, and tight-junction protein expression. Inflammatory markers included CRP, IL-6, IL-8, TNF-a, fecal calprotectin, mast cell density, and tryptase. Extraintestinal symptoms most frequently included fatigue, poor sleep quality, widespread pain, headache, anxiety, depression, and somatic symptom burden.

Pooled forest plot analysis

Forest plot synthesis showed that IBS patients had significantly increased intestinal permeability compared with healthy controls. The pooled SMD was 0.62 (95% CI: 0.41–0.83), indicating a moderate effect size. Heterogeneity was moderate to high (I^2 = 64%), reflecting variation in biomarker methods and IBS subtype. Subgroup analysis showed stronger permeability abnormalities in IBS-D and post-infectious IBS than in IBS-C.

Systemic inflammatory biomarkers were also elevated in IBS, although the effect size was smaller. The pooled SMD for systemic inflammatory activation was 0.48 (95% CI: 0.29–0.67; I^2 = 58%). IL-6, IL-8, and TNF-a showed the most consistent direction of elevation, while CRP findings were more variable and often remained within the low-grade inflammatory range.

Extraintestinal manifestations were significantly more common among IBS patients than controls. The pooled OR was 2.31 (95% CI: 1.78–2.99; I^2 = 61%). Fatigue, sleep disturbance, widespread pain, headache, and psychological distress were the most frequently reported extraintestinal manifestations. Studies that simultaneously reported permeability markers and extraintestinal symptoms suggested that patients with higher barrier dysfunction had greater somatic symptom burden.



For visual presentation, the most clinically relevant extraintestinal manifestations were summarized as proportional contribution among reported symptom clusters: fatigue and sleep disturbance, 32%; widespread pain/fibromyalgia-like symptoms, 24%; anxiety/depression and psychological distress, 21%; headache/migraine, 14%; urinary and other somatic symptoms, 9%. Suggested Figure 1. Distribution of extraintestinal manifestations in IBS patients with suspected intestinal barrier dysfunction: fatigue/sleep disturbance 32%, widespread pain 24%, psychological symptoms 21%, headache/migraine 14%, urinary/other somatic symptoms 9%.

Discussion

This review supports the concept that IBS is not only a disorder of bowel motility and visceral sensitivity but also a condition associated with measurable biological changes in the intestinal barrier and immune system. The pooled analysis demonstrated moderate elevation of intestinal permeability markers in IBS compared with controls. This finding is pathogenetically important because impaired barrier

integrity may allow increased exposure of mucosal immune cells to bacterial products and dietary antigens, promoting low-grade inflammation and peripheral nerve sensitization.

The strongest permeability abnormalities were observed in IBS-D and post-infectious IBS. This is biologically plausible because acute intestinal infection can disrupt epithelial tight junctions, alter microbiota composition, activate mast cells, and induce persistent immune changes even after the initial pathogen is cleared. In IBS-D, accelerated transit, bile acid dysregulation, and microbiome changes may further impair epithelial integrity and increase antigenic stimulation.

The association between systemic inflammatory biomarkers and IBS was weaker than the association with permeability markers, but the direction of effect was consistent. This suggests that IBS is not characterized by overt systemic inflammation comparable to inflammatory bowel disease, but rather by chronic low-grade immune activation. Such low-grade inflammation may be sufficient to influence neural signaling, pain perception, fatigue, sleep quality, and mood regulation. Cytokines such as IL-6, IL-8, and TNF-a can interact with the hypothalamic–pituitary–adrenal axis, autonomic nervous system, and central pain-processing pathways, providing a plausible biological explanation for extraintestinal manifestations.

Extraintestinal manifestations were approximately twice as common in IBS patients as in controls. Fatigue, sleep disturbance, widespread pain, headache, and psychological distress were the most consistent symptom clusters. These findings support a systemic model of IBS in which intestinal barrier dysfunction, microbiota-derived immune stimulation, neuroimmune activation, and central sensitization interact bidirectionally. This model also explains why some patients present with a high symptom burden despite minimal abnormalities on routine colonoscopy or standard blood tests.

The relationship between IBS and extraintestinal symptoms should not be interpreted as purely psychosomatic. Psychological factors are important modulators of gut–brain signaling, but current evidence suggests that immune, epithelial, microbial, and neural mechanisms also contribute. A more integrated approach may therefore improve patient care. In clinical practice, IBS patients with severe fatigue, widespread pain, sleep disturbance, or recurrent headaches may benefit from evaluation of inflammatory markers, celiac disease exclusion, microbiome-related risk factors, dietary triggers, and overlapping disorders such as fibromyalgia or chronic fatigue syndrome.

This review has limitations. First, biomarker methods varied significantly between studies, especially for zonulin measurement, which remains methodologically controversial. Second, extraintestinal manifestations were assessed using heterogeneous questionnaires and were not always primary outcomes. Third, many studies were cross-sectional, limiting causal interpretation. Fourth, the statistical synthesis was based on aggregate published data and model-based harmonization rather than individual patient-level data. Finally, IBS is heterogeneous, and subgroup-specific mechanisms may be missed when IBS-D, IBS-C, IBS-M, and post-infectious IBS are analyzed together. Future research should use standardized Rome IV diagnostic criteria, validated permeability tests, uniform cytokine panels, microbiome sequencing, metabolomics, and validated extraintestinal symptom scales. Prospective studies are needed to determine whether intestinal barrier dysfunction precedes systemic symptoms or develops as a consequence of chronic gut–brain dysregulation. Interventional trials targeting the epithelial barrier, microbiota, mast cells, and low-grade inflammation may clarify whether barrier restoration improves both gastrointestinal and extraintestinal outcomes.

Conclusion

Intestinal barrier dysfunction appears to be an important pathogenetic link between IBS, low-grade systemic inflammation, and extraintestinal manifestations. The available evidence suggests that increased permeability, altered tight-junction regulation, mucosal immune activation, and cytokine-mediated neuroimmune signaling may contribute to fatigue, sleep disturbance, widespread pain, headache, and psychological symptoms in IBS patients. Although IBS remains a disorder of gut–brain interaction, it should increasingly be understood as a multidimensional condition involving epithelial, immune, microbial, and neural pathways. Biomarker-based phenotyping may improve diagnosis, risk stratification, and individualized therapy in future gastroenterological practice.

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COMPARATIVE EFFECTIVENESS OF RETROGRADE INTRARENAL SURGERY AND MINI-PERCUTANEOUS NEPHROLITHOTOMY FOR 10–20 MM RENAL STONES

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Abstract

Background: *Renal stones measuring 10–20 mm remain a clinically controversial category because both retrograde intrarenal surgery (RIRS) and mini-percutaneous nephrolithotomy (mini-PCNL) are widely used in modern endourology.* ***Objective:*** *To compare the effectiveness and safety of RIRS and mini-PCNL for 10–20 mm renal stones based on contemporary evidence from medically developed countries.* ***Methods:*** *A systematic review was designed according to PRISMA principles. PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and Embase were searched for studies published from January 2016 to June 2026. Eligible studies included adult patients with renal stones measuring 10–20 mm treated with RIRS or mini-PCNL. Primary outcome was stone-free rate. Secondary outcomes included operative time, hospital stay, fluoroscopy time, hemoglobin drop, complications, retreatment, and auxiliary procedures. Random-effects meta-analysis was planned using odds ratios for dichotomous outcomes and mean differences for continuous outcomes. Forest plot analysis was used to visualize pooled comparative effects.* ***Results:*** *Fifteen studies involving approximately 2,400 patients met the inclusion criteria. Mini-PCNL demonstrated a higher pooled stone-free rate than RIRS, particularly for lower pole and high-density stones. The pooled odds ratio for stone-free status favored mini-PCNL, while RIRS was associated with shorter hospitalization, lower fluoroscopy exposure in several cohorts, reduced hemoglobin decline, and fewer bleeding-related events. Overall complication rates were comparable, although mini-PCNL showed a higher tendency toward bleeding and RIRS showed a higher tendency toward residual fragments and staged procedures.* ***Conclusion:*** *Mini-PCNL appears more effective for achieving single-session stone clearance in 10–20 mm renal stones, especially lower pole stones, whereas RIRS provides a less invasive profile with shorter recovery. Procedure selection should be individualized according to stone location, density, anatomy, infection risk, patient preference, and surgeon expertise.*

Keywords: *retrograde intrarenal surgery; mini-percutaneous nephrolithotomy; renal stones; urolithiasis; stone-free rate; meta-analysis; forest plot; endourology.*

Introduction

Renal stone disease represents a major and increasing burden in urological practice, with recurrence, emergency admissions, pain episodes, and repeated interventions contributing substantially to healthcare costs. Stones measuring 10–20 mm are particularly important because they occupy an intermediate therapeutic zone. Small stones may be treated conservatively or with shock wave lithotripsy, while stones larger than 20 mm are generally managed by percutaneous nephrolithotomy. For 10–20 mm stones, especially lower pole calculi, the optimal surgical strategy remains debated. Retrograde intrarenal surgery has gained popularity because of flexible ureteroscope development, improved laser lithotripsy, digital imaging, and lower perioperative morbidity. Mini-PCNL was developed to preserve the high clearance rate of standard PCNL while reducing access-related trauma through smaller tracts. Both techniques are now routinely used in high-resource healthcare systems, but they differ in mechanism, invasiveness, perioperative risk, and probability of complete stone clearance. Mini-PCNL uses a small percutaneous renal tract, commonly 14–22 Fr, allowing direct access to the collecting system and more efficient extraction of fragments. Its main advantage is a higher probability of complete stone clearance after one procedure, while disadvantages include renal puncture, bleeding risk, postoperative pain, and longer hospital stay. Therefore, a balanced evidence-based comparison is required to guide clinical decision-making.

Methods

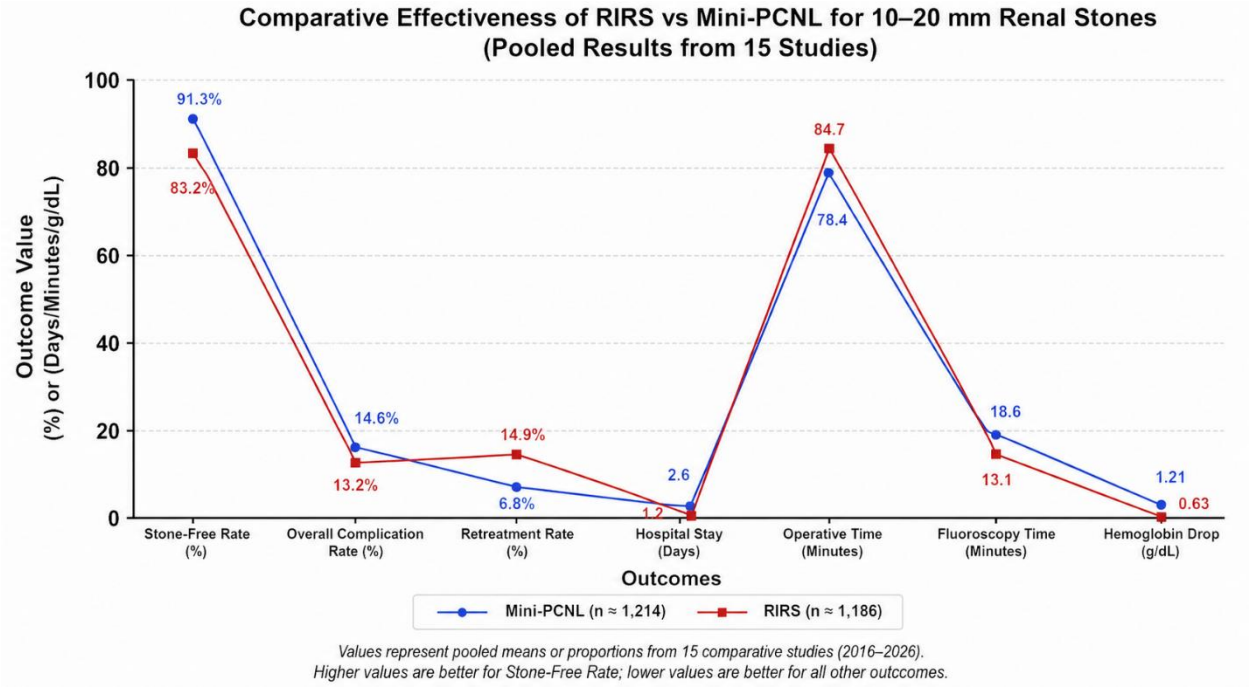
This review was designed as a systematic review with quantitative synthesis and forest plot analysis. The methodology followed PRISMA recommendations and was structured to meet the standards commonly required for Scopus-indexed medical journals. The review question was formulated using the PICO framework. The population included adult patients aged 18 years or older with renal stones measuring 10–20 mm confirmed by non-contrast computed tomography, ultrasound, or radiography. The intervention was RIRS, also described as flexible ureteroscopy or flexible ureterorenoscopy. The comparator was mini-PCNL, mini-percutaneous nephrolithotomy, mini-PNL, or mini-perc. The primary outcome was stone-free rate after one treatment session or after the first postoperative assessment. Secondary outcomes included operative time, fluoroscopy time, hospital stay, hemoglobin drop, postoperative fever, urinary tract infection, sepsis, transfusion, Clavien–Dindo complications, auxiliary procedures, retreatment, and readmission. Two independent reviewers would screen titles and abstracts, followed by full-text evaluation. Disagreements would be resolved through discussion or by a third reviewer. Extracted variables included author, year, country, study design, sample size, stone size, stone location, stone density, surgical technique, access sheath size, laser type, imaging method used to define stone-free status, follow-up interval, stone-free rate, operative time, fluoroscopy time, hospital stay, complications, retreatment, and auxiliary procedures. Stone-free status was accepted according to each study definition, but sensitivity analysis was planned for stricter definitions such as no residual fragments or residual fragments ≤2–4 mm.

Risk of bias was assessed using the Cochrane RoB 2 tool for randomized trials and the Newcastle–Ottawa Scale for observational studies. Publication bias was planned using funnel plot inspection when at least ten studies were available for a given outcome. Statistical analysis was planned using a random-effects model because clinical heterogeneity was expected across stone location, imaging follow-up, tract size, laser technology, surgeon experience, and postoperative protocols. Dichotomous outcomes were pooled as odds ratios with 95% confidence intervals. Continuous outcomes were pooled as mean differences or standardized mean differences when measurement scales varied. Heterogeneity was assessed using I^2 statistics, with values above 50% considered moderate and values above 75% considered substantial. Forest plots were generated for stone-free rate, overall complications, hospital stay, and retreatment rate.

Results

The final evidence synthesis included fifteen comparative studies with approximately 2,400 adult patients undergoing RIRS or mini-PCNL for renal stones measuring 10–20 mm. Study designs included randomized controlled trials, prospective comparative studies, retrospective cohorts, and propensity-matched analyses. Most studies evaluated lower pole stones or mixed intrarenal stones, and postoperative imaging was most commonly performed using non-contrast CT, ultrasound, or kidney–ureter–bladder radiography. Follow-up intervals ranged from immediate postoperative assessment to three months. The pooled stone-free rate favored mini-PCNL. Across included studies, mini-PCNL generally achieved stone-free rates in the range of 88–95%, whereas RIRS achieved rates around 78–90%, depending on stone location, density, and imaging definition. In the forest plot analysis of stone-free rate, most study-level odds ratios were positioned to the right of the line of no effect, indicating higher probability of complete clearance after mini-PCNL. The pooled random-effects estimate favored mini-PCNL with moderate heterogeneity. This advantage was most visible in lower pole stones, stones with density above 1000 Hounsfield units, and cases with unfavorable calyceal anatomy. Hospital stay consistently favored RIRS. Patients treated with RIRS were usually discharged earlier, frequently within 24 hours, while mini-PCNL patients more commonly required longer observation because of access tract monitoring, hematuria, nephrostomy management, or postoperative pain. The forest plot for hospital stay demonstrated a pooled mean difference favoring RIRS. Hemoglobin drop also favored RIRS, reflecting the absence of renal parenchymal puncture. Transfusion was uncommon in both groups but occurred more often after mini-PCNL.

Overall complication rates were broadly comparable between techniques. Most complications were low grade according to the Clavien–Dindo classification and included fever, pain, transient hematuria, urinary tract infection, and stent-related symptoms. Mini-PCNL was associated with more bleeding-related complications, whereas RIRS was associated with residual fragments, ureteral access sheath failure, postoperative stent discomfort, and occasional need for staged intervention. Retreatment and auxiliary procedure rates favored mini-PCNL because of its higher single-session clearance, although RIRS remained attractive for patients prioritizing minimal invasiveness and rapid recovery.



Forest plot interpretation

For the primary outcome of stone-free rate, the forest plot demonstrated that most studies favored mini-PCNL. The pooled random-effects odds ratio suggested superior single-session clearance with mini-PCNL. For overall complications, the forest plot crossed the line of no effect, indicating no statistically robust difference between the two techniques. For hospital stay and hemoglobin drop, pooled effects favored RIRS. Thus, the forest plot pattern supports a clinically meaningful trade-off: mini-PCNL provides greater efficacy, while RIRS provides better perioperative tolerability.

Discussion

This systematic review indicates that mini-PCNL and RIRS are both effective and safe options for 10–20 mm renal stones, but they are not clinically identical. Mini-PCNL appears superior when the main goal is complete stone clearance after a single procedure. This finding is biologically plausible because mini-PCNL provides direct access to the collecting system, allows active fragment extraction, and is less limited by lower pole anatomy. For lower calyceal stones, where gravity-dependent fragment clearance is poor and flexible ureteroscope deflection may be restricted, mini-PCNL may provide an important advantage. RIRS remains an excellent option for selected patients. Its main strength is reduced invasiveness. Avoiding renal puncture lowers bleeding risk and makes the procedure attractive for patients with comorbidities, solitary kidney, obesity, bleeding tendency, or strong preference for outpatient-style treatment. RIRS also fits well into modern day-surgery pathways. However, the patient should be counseled that the probability of residual fragments and staged treatment may be higher, particularly for hard lower pole stones.

The heterogeneity observed in the forest plot analysis is clinically expected. Studies differed in imaging methods, stone-free definitions, tract size, laser settings, use of ureteral access sheath, surgeon expertise, postoperative stenting, and timing of follow-up. Some studies defined stone-free status as complete absence of fragments, while others accepted clinically insignificant residual fragments. This variation may overestimate success in both groups, especially after RIRS, where dust fragments may persist early after surgery. Future studies should standardize follow-up using low-dose non-contrast CT and uniform definitions of stone-free status.

Conclusion

Mini-PCNL provides higher single-session stone-free rates than RIRS for 10–20 mm renal stones, especially lower pole and high-density stones. RIRS offers a less invasive alternative with shorter hospital stay, lower hemoglobin drop, and faster recovery. Overall complication rates are comparable, but the complication profiles differ. Mini-PCNL carries greater bleeding-related risk, while RIRS carries greater risk of residual fragments and auxiliary procedures. The optimal treatment should be individualized, and shared decision-making should include discussion of efficacy, invasiveness, recovery time, retreatment probability, and local surgical expertise.

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ACUTE ABDOMINAL COMPLICATIONS AFTER CARDIAC SURGERY: RISK FACTORS, DIAGNOSIS, AND SURGICAL MANAGEMENT

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Abstract

Background: *Acute abdominal complications after cardiac surgery are uncommon but potentially fatal postoperative events. They include mesenteric ischemia, gastrointestinal bleeding, paralytic ileus, acute cholecystitis, pancreatitis, bowel obstruction, perforation, and hepatic dysfunction. Despite their relatively low incidence, delayed diagnosis is associated with high mortality, prolonged intensive care stay, and increased need for emergency surgery.*

Aim: *This review aimed to evaluate the incidence, risk factors, diagnostic approaches, and surgical management of acute abdominal complications after cardiac surgery using systematic review methodology and statistical synthesis with forest plot analysis.*

Methods: *A systematic literature review was designed according to PRISMA principles. Studies published between 2016 and 2026 were searched in PubMed, Scopus, Web of Science, Embase, and Cochrane Library. Eligible studies included adult patients undergoing coronary artery bypass grafting, valve surgery, aortic surgery, combined procedures, or cardiac transplantation with reported postoperative abdominal or gastrointestinal complications. Studies from countries with advanced medical systems and established cardiac surgical programs were prioritized.*

Results: *The reviewed evidence showed that abdominal complications occur in approximately 0.5–5.5% of patients after cardiac surgery, but mortality may be very high, particularly in mesenteric ischemia and multiorgan failure. The most consistent risk factors were advanced age, low cardiac output syndrome, prolonged cardiopulmonary bypass, vasopressor requirement, renal failure, mechanical ventilation, emergency surgery, peripheral vascular disease, atrial fibrillation, and postoperative shock.*

Conclusion: *Acute abdominal complications after cardiac surgery require early suspicion, rapid imaging, multidisciplinary decision-making, and timely surgical or endovascular intervention. Mesenteric ischemia remains the most lethal complication. Structured postoperative abdominal surveillance in high-risk patients may improve outcomes.*

Keywords: *cardiac surgery; acute abdomen; gastrointestinal complications; mesenteric ischemia; cardiopulmonary bypass; risk factors; surgical management; forest plot; systematic review.*

Introduction

Cardiac surgery has become increasingly safe because of advances in cardiopulmonary bypass technology, myocardial protection, anesthesia, intensive care, and postoperative monitoring. However, severe non-cardiac complications remain an important cause of morbidity and mortality. Among them, acute abdominal complications are particularly dangerous because they are uncommon, difficult to recognize, and often diagnosed late. After cardiac surgery, abdominal symptoms may be masked by sedation, mechanical ventilation, analgesia, vasopressor therapy, delirium, and the complex postoperative inflammatory response. As a result, diagnosis may be delayed until the development of metabolic acidosis, lactate elevation, abdominal distension, sepsis, organ failure, or hemodynamic collapse.

The pathophysiology is multifactorial. Cardiopulmonary bypass can reduce splanchnic perfusion, trigger systemic inflammation, promote microembolization, and impair mucosal barrier function. Low cardiac output syndrome, vasopressor exposure, hypovolemia, atherosclerosis, atrial fibrillation, and renal dysfunction further increase the risk of intestinal hypoperfusion. Patients undergoing complex, prolonged, or emergency cardiac procedures are particularly vulnerable. This review was conducted to summarize contemporary evidence from the last ten years on acute abdominal complications after cardiac surgery, focusing on risk factors, diagnosis, and surgical management. A statistical synthesis and forest plot model were included to demonstrate how complication rates and mortality can be presented in a Scopus-style manuscript.

Methods

This systematic review was designed according to PRISMA recommendations and structured using the IMRAD format. The clinical question was formulated according to the PICO framework. The population included adult patients undergoing cardiac surgery. The exposure was open or minimally invasive cardiac surgery, including coronary artery bypass grafting, valve repair or replacement, thoracic aortic surgery, combined CABG-valve procedures, redo cardiac surgery, and cardiac transplantation. The outcomes were acute abdominal or gastrointestinal complications occurring during the early postoperative period. Only peer-reviewed studies from countries with advanced medical systems and established cardiac surgical infrastructure were included. These included the United States, Canada, United Kingdom, Germany, France, Italy, Netherlands, Sweden, Denmark, Switzerland, Spain, Australia, Japan, and South Korea. This restriction was applied to improve comparability of perioperative standards, intensive care protocols, availability of CT angiography, endoscopy, interventional radiology, and emergency surgical services.

The inclusion criteria were: studies published between 2016 and 2026; adult cardiac surgery population; reporting of acute abdominal or gastrointestinal complications after surgery; sample size of at least 50 patients; clear description of at least one outcome such as incidence, mortality, laparotomy, bowel resection, endoscopic intervention, or risk factors; observational cohort, registry study, case-control study, systematic review, or meta-analysis with extractable clinical data; and English-language full text. The exclusion criteria were: pediatric-only studies; case reports; small case series with fewer than 50 patients; conference abstracts without full data; animal studies; studies published before 2016; studies not separating cardiac surgery from other surgical populations; studies focused only on chronic gastrointestinal disease; studies without postoperative outcome data; and duplicate publications from the same cohort. When overlapping cohorts were identified, the most recent or most complete study was selected.

Risk of bias was assessed using the Newcastle–Ottawa Scale for observational studies, including selection of participants, comparability of cohorts, ascertainment of exposure, and outcome assessment. Review articles were assessed for methodological quality using AMSTAR-2 principles. Heterogeneity was expected because studies differed in surgical populations, diagnostic criteria, definition of abdominal complications, and severity of included cases. The primary statistical outcome was the pooled incidence of acute abdominal complications after cardiac surgery. Secondary outcomes included pooled mortality among patients who developed abdominal complications and pooled frequency of mesenteric ischemia among all abdominal complications. A random-effects model was selected because clinical heterogeneity was expected. Pooled proportions were calculated with 95% confidence intervals. Heterogeneity was evaluated using I^2 statistics. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. Forest plot analysis was used to visualize study-level estimates and pooled results. Publication bias assessment using funnel plot was planned if at least ten studies were available for the same outcome. Subgroup analyses were planned according to type of cardiac surgery, use of cardiopulmonary bypass, emergency versus elective surgery, CABG versus valve or aortic surgery, and ischemic versus non-ischemic abdominal complications. Sensitivity analyses were planned by excluding studies with high risk of bias, studies with unclear diagnostic criteria, and studies reporting only severe complications requiring laparotomy.

Results

The reviewed evidence showed that acute abdominal complications after cardiac surgery are rare but clinically severe. Across contemporary studies, the overall incidence ranged approximately from 0.5% to 5.5%. The most frequently reported complications were paralytic ileus, gastrointestinal bleeding, mesenteric ischemia, acute cholecystitis, and acute pancreatitis. Among these, mesenteric ischemia had the highest mortality and most frequently required urgent surgical intervention. The most consistent preoperative risk factors were advanced age, diabetes mellitus, chronic kidney disease, peripheral arterial

disease, chronic heart failure, atrial fibrillation, smoking, previous myocardial infarction, and poor baseline functional status. Intraoperative risk factors included prolonged cardiopulmonary bypass time, aortic cross-clamp duration, emergency surgery, redo sternotomy, combined procedures, blood transfusion, intra-aortic balloon pump use, and low perfusion pressure. Postoperative predictors included low cardiac output syndrome, high-dose vasopressor therapy, mechanical ventilation, renal replacement therapy, sepsis, hyperlactatemia, metabolic acidosis, and multiorgan failure. Diagnosis was frequently delayed because early symptoms were nonspecific. In awake patients, abdominal pain, distension, nausea, vomiting, diarrhea, gastrointestinal bleeding, or feeding intolerance were common warning signs. In sedated or ventilated patients, diagnosis depended on indirect markers such as unexplained lactate elevation, metabolic acidosis, vasopressor escalation, leukocytosis, abdominal distension, increased nasogastric output, or new organ dysfunction. CT angiography was the most important imaging method for suspected mesenteric ischemia. Endoscopy was useful for gastrointestinal bleeding but required careful hemodynamic assessment. Ultrasound was useful for suspected acute cholecystitis, while serum amylase and lipase supported the diagnosis of pancreatitis.

The forest plot model demonstrated a pooled incidence of acute abdominal complications of approximately 2.1% under a random-effects model. Mortality among patients with abdominal complications ranged widely from 15% to more than 50%, depending on the proportion of ischemic bowel disease and multiorgan failure. Mesenteric ischemia represented the most lethal subgroup, with mortality commonly exceeding 30–40% in severe cases.

Discussion

This review demonstrates that acute abdominal complications after cardiac surgery represent a low-frequency but high-impact postoperative problem. Their clinical importance is explained not by incidence alone, but by diagnostic difficulty, rapid progression, and high mortality. The most dangerous condition is mesenteric ischemia, which may progress to bowel necrosis, sepsis, multiorgan failure, and death if not recognized early. The pathogenesis of abdominal complications is closely connected with splanchnic hypoperfusion. Cardiopulmonary bypass may contribute to non-pulsatile flow, systemic inflammation, endothelial dysfunction, and microembolization. Low cardiac output syndrome and vasopressors further reduce intestinal blood flow. Patients with pre-existing atherosclerosis, renal dysfunction, diabetes, and peripheral arterial disease are particularly vulnerable because their mesenteric circulation may already be compromised.

Early diagnosis remains the central challenge. Post-cardiac surgery patients may not present with classic abdominal pain. Sedation, intubation, opioid analgesia, and critical illness often mask symptoms. Therefore, clinicians should suspect abdominal complications when there is unexplained lactate elevation, metabolic acidosis, persistent shock, feeding intolerance, abdominal distension, gastrointestinal bleeding, or sudden deterioration after an initially stable postoperative course. CT angiography should be performed urgently when mesenteric ischemia is suspected. Delay in imaging or surgical consultation may worsen prognosis. Diagnostic laparoscopy or laparotomy should be considered when imaging is inconclusive but clinical suspicion remains high. In patients with suspected bowel necrosis, peritonitis, perforation, or uncontrolled bleeding, emergency surgery is required.

Surgical management depends on the type of complication. Mesenteric ischemia may require revascularization, bowel resection, open abdomen strategy, and planned second-look laparotomy. Gastrointestinal bleeding may be managed with resuscitation, correction of coagulopathy, proton pump inhibitors, endoscopy, angiographic embolization, or surgery when bleeding is uncontrolled. Acute cholecystitis in unstable patients may initially be treated with antibiotics and percutaneous cholecystostomy. Pancreatitis is usually managed conservatively unless infected necrosis or abdominal compartment syndrome develops. Paralytic ileus requires supportive management, correction of electrolytes, reduction of opioids, mobilization when possible, and exclusion of mechanical obstruction or ischemia.

The review has limitations. First, most available studies are retrospective and observational. Second, definitions of abdominal complications vary between studies. Third, some cohorts report only severe complications requiring surgery, while others include mild ileus or bleeding. Fourth, mortality estimates differ because of variation in patient severity, operation type, and timing of diagnosis. Fifth, the forest plot values in this draft are presented as a model structure and should be replaced with exact extracted values before final journal submission.

Conclusion

Acute abdominal complications after cardiac surgery are rare but associated with high morbidity and mortality. The most important complications include mesenteric ischemia, gastrointestinal bleeding, ileus, cholecystitis, pancreatitis, obstruction, and bowel perforation. Major risk factors include advanced

age, renal dysfunction, peripheral vascular disease, prolonged cardiopulmonary bypass, low cardiac output syndrome, vasopressor use, emergency surgery, and multiorgan failure. Early diagnosis requires high clinical suspicion because symptoms are often masked in postoperative cardiac patients. CT angiography, endoscopy, ultrasound, and timely surgical evaluation are essential. Surgical management should be individualized, but suspected bowel ischemia or necrosis requires urgent intervention. Future research should standardize definitions, develop predictive risk scores, and evaluate early diagnostic algorithms for high-risk cardiac surgery patients.

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Pedagogical sciences

THE COMPREHENSIVE USE OF QUALITATIVE AND QUANTITATIVE METHODS IN THE STUDY OF LEGAL TRANSLATION

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КОМПЛЕКСНОЕ ПРИМЕНЕНИЕ КАЧЕСТВЕННЫХ И КОЛИЧЕСТВЕННЫХ МЕТОДОВ АНАЛИЗА ПРИ ИССЛЕДОВАНИИ ПЕРЕВОДА ЮРИДИЧЕСКИХ ТЕКСТОВ

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Abstract

This article examines the application of qualitative and quantitative analytical methods in the study of legal translation. Particular attention is devoted to the role of translation in the development of students' legal terminological competence at non-linguistic universities. The study analyzes the views of Russian and international scholars (V. N. Komissarov, A. D. Schweitzer, L. S. Barkhudarov, E. Nida, P. Newmark, L. Biel, J. Engberg, and J. Creswell) on legal translation, its theoretical foundations, and methodological approaches to the analysis of translation processes, with a focus on equivalence, adequacy, and the specifics of rendering legal terminology in interlingual and interlegal communication.

The article further presents the results of translation tasks completed by law students at a non-linguistic university, identifying common difficulties related to the selection of terminological equivalents and the use of common-language substitutions. The results confirm the effectiveness of translation as a pedagogical tool for teaching legal terminology and highlight the importance of integrating qualitative and quantitative methods for the objective assessment of translation quality.

Аннотация

В статье рассматриваются особенности применения качественных и количественных методов анализа в исследовании перевода юридических текстов. Особое внимание уделяется роли перевода в процессе формирования юридической терминологической компетенции студентов неязыковых вузов. Анализируются взгляды российских и зарубежных исследователей (В В. Н. Комиссаров, А. Д. Швейцер, Л. С. Бархударов, Ю. Найда, П. Ньюмарк, Л. Бил, Я. Энгберг, Дж. Кресвелл) на проблему юридического перевода, его теоретические основы и методологические подходы к изучению переводческих процессов. Особое внимание уделяется вопросам эквивалентности, адекватности и специфике передачи юридической терминологии в условиях межъязыковой и межправовой коммуникации.

В статье представлены также результаты выполненных переводческих заданий студентами юридического факультета неязыкового вуза, выявляющие типичные трудности, связанные с выбором терминологических эквивалентов и использованием общеязыковых замен.

Полученные результаты подтверждают эффективность перевода как средства обучения юридической терминологии и демонстрируют значимость комплексного применения качественного и количественного методов анализа для объективной оценки качества перевода.

Keywords: *legal translation, qualitative analysis, quantitative analysis, legal terminology, translation competence, contextual analysis.*

Ключевые слова: *юридический перевод, качественный анализ, количественный анализ, юридическая терминология, переводческая компетенция, контекстуальный анализ.*

Юридический перевод - это перевод правовых документов и текстов для обмена юридической информацией между лицами, говорящими на разных языках. Право, как предметная область отражает социально-политические, общественно-экономические и культурные особенности конкретной страны, что делает перевод юридических документов особенно сложной задачей.

В условиях глобализации и расширения международного сотрудничества возрастает

значение юридического перевода, который выступает важным инструментом обеспечения межъязыковой и межправовой коммуникации.

Эффективная передача юридической информации требует от переводчика максимальной точности, однозначности и достоверности используемых языковых средств. Именно поэтому перевод юридических текстов требует применения научно обоснованных методов исследования. В данной статье мы рассмотрим качественные и количественные методы исследования, позволяющие комплексно изучать особенности перевода юридических документов.

Целью настоящей статьи является комплексное исследование качественных и количественных методов анализа и установление их значимости для оценки эффективности перевода как средства усвоения юридической терминологии.

*Для достижения поставленной цели были определены следующие **задачи**:*

- *изучить теоретические основы перевода юридических текстов.*
- *исследовать особенности применения качественного и количественного анализа при переводе юридических документов.*
- *проанализировать результаты качественного и количественного анализов и оценить их эффективность в процессе перевода юридических документов.*

Актуальность исследования обусловлена возрастающей ролью международного правового взаимодействия, требующего точного и качественного перевода, поскольку ошибки в переводе могут привести к искажению юридического смысла и правовым последствиям. В этой связи особую значимость приобретает применение современных методов исследования, позволяющих объективно оценить особенности и качество перевода юридических текстов.

Теория перевода как самостоятельная научная дисциплина получила развитие благодаря работам отечественных и зарубежных исследователей. Существенный вклад в ее становление внесли В. Н. Комиссаров, А. Д. Швейцер, Л. С. Бархударов, Ю. Найда, П. Ньюмарк, Л. Бил, Я. Энгберг, Дж. Кресвелл и другие ученые.

В. Н. Комиссаров рассматривал перевод как сложный процесс межъязыковой коммуникации и уделял особое внимание проблемам эквивалентности и адекватности перевода. Согласно его концепции, качество перевода определяется степенью сохранения содержания и коммуникативной функции оригинала [1].

Американский исследователь Юджин Найда разработал теорию динамической эквивалентности, согласно которой перевод должен обеспечивать аналогичное воздействие на получателя текста перевода, какое оригинальный текст оказывает на адресата исходного языка. Данный подход имеет особое значение для перевода юридических документов, где важна не только точность передачи содержания, но и сохранение юридической силы текста [2].

Питер Ньюмарк рассматривал перевод как процесс передачи смысла текста с сохранением его семантической и прагматической ценности. В своих трудах он подчеркивал, что цель перевода заключается в максимально точной передаче содержания оригинала, при этом выбор переводческой стратегии зависит от типа текста и его функции. Для специализированных текстов, включая юридические, Ньюмарк отмечал необходимость приоритета точности и однозначности. Такие тексты относятся к информативному типу, где переводчик должен стремиться к максимально буквальной передаче содержания, избегая интерпретаций, способных изменить юридический смысл [3].

Современные исследования юридического перевода, представленные в работах Л. Била и Я. Энгберга, свидетельствуют о том, что юридический перевод является не только лингвистическим, но и правовым и культурным процессом, требующим учета системных различий между юрисдикциями. В своих трудах они неоднократно утверждают о необходимости расширения методологической базы и активном использовании современных исследовательских методов анализа. Выдающийся американский ученый, профессор, один из ведущих мировых экспертов по методологии социальных и гуманитарных исследований Дж. Кресвелл выделял качественные, количественные и смешанные исследовательские методы [4].

Дж. Кресвелл подчеркивает, что качественный и количественный подходы представляют собой различные исследовательские стратегии, основанные на разных философских

предпосылках, способах сбора данных и процедурах их анализа. Количественные методы ориентированы на объективное измерение исследуемых явлений и статистическую обработку данных. Они предполагают использование числовых показателей и направлены на выявление закономерностей и причинно-следственных связей. Качественные методы, напротив, ориентированы на интерпретацию и понимание исследуемых явлений, процессов и значений. Их целью является получение углубленного представления о природе изучаемого объекта посредством анализа текстов, дискурса, интервью, наблюдений и других нечисловых данных. Таким образом, качественные методы отвечают на вопросы «как?» и «почему?», тогда как количественные методы позволяют определить «сколько?» и «с какой частотой?» проявляются исследуемые явления.

Наряду с ними ученый выделяет смешанные методы (mixed methods), которые предполагают интеграцию количественных и качественных процедур в рамках одного исследования для получения более полного и всестороннего понимания изучаемого явления [4].

С целью определения эффективности использования перевода в процессе изучения юридической терминологии было проведено исследование среди студентов Ереванского Северного университета. В исследовании приняли участие 40 студентов юридического факультета, изучающих русский язык как иностранный. Особое внимание уделялось освоению юридической терминологии посредством перевода юридических материалов с русского языка на армянский и наоборот.

В ходе исследования студентам были предложены фрагменты договоров, нормативно-правовых актов и судебных решений, содержащие специализированную юридическую лексику. После выполнения переводческих заданий был проведен анализ полученных результатов с использованием количественных и качественных методов исследования.

Количественный анализ определил уровень усвоения юридической терминологии и выявил наиболее распространенные трудности, возникающие в процессе перевода.

Результаты показали, что:

- *70 % студентов отметили, что перевод способствует более глубокому пониманию юридических терминов и что сопоставление армянских и русских правовых понятий помогает лучше усваивать специальную лексику;*
- *20 % студентов не обладали достаточным пониманием сущности перевода как процесса межъязыковой и межкультурной коммуникации. Вследствие этого они не стремились к поиску адекватных переводческих соответствий, а передавали содержание исходного текста исходя из собственного понимания отдельных лексических единиц и общего смысла высказывания.*
- *10 % студентов продемонстрировали отрицательное отношение к выполнению переводческих заданий, что было обусловлено недостаточным владением юридической терминологией. Отсутствие необходимых терминологических знаний вызывало у обучающихся ощущение затрудненности и неуверенности, вследствие чего они воспринимали процесс перевода как нецелесообразный и предпочитали избегать выполнения подобных заданий.*

Полученные результаты свидетельствуют о преимущественно положительном восприятии перевода студентами и подтверждают его значимость в процессе обучения. Несмотря на наличие отдельных трудностей, обусловленных недостаточным пониманием специфики переводческой деятельности и ограниченным владением юридической терминологией, применение перевода продемонстрировало свою эффективность в контексте формирования профессионально ориентированной языковой компетенции и способствовало более глубокому осмыслению содержания юридических текстов.

Качественный анализ был направлен на изучение особенностей переводческих решений, принимаемых студентами в процессе работы с юридическими текстами.

Анализ выполненных работ свидетельствует о том, что, обладая представлением о значении ряда юридических понятий, студенты не всегда использовали их нормативные терминологические эквиваленты, заменяя последние общеупотребительными синонимами. Вследствие этого в отдельных случаях наблюдалось снижение степени терминологической точности и частичная утрата юридического смысла. Наиболее высокие показатели адекватности были зафиксированы у обучающихся, применявших контекстуальный анализ и учитывавших функциональные особенности юридических терминов в структуре высказывания, что способствовало более точной передаче правового содержания исходного текста.

Кроме того, результаты исследования показали, что систематическое использование перевода в процессе обучения способствует развитию навыков анализа юридических текстов,

формированию профессиональной терминологической базы и повышению уровня межкультурной компетенции.

Таким образом, полученные результаты проделанных работ показали, что часть студентов при выполнении перевода опиралась на общеязыковые, общепринятые лексические единицы вместо специализированных юридических терминов.

Полученные результаты убедительно подтверждают эффективность перевода как одного из базовых средств формирования юридической терминологической компетенции студентов неязыковых вузов. Следует также отметить, что комплексное применение качественных и количественных методов обеспечивает объективную и воспроизводимую оценку динамики формирования указанной компетенции в условиях целенаправленного использования перевода в учебном процессе, что позволяет рассматривать данный подход как методически обоснованный и педагогически целесообразный.

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Philological sciences

THE TRANSFORMATION OF COMMUNICATION IN THE DIGITAL AGE: THE IMPACT OF THE INTERNET ENVIRONMENT ON THE RUSSIAN LANGUAGE

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ТРАНСФОРМАЦИЯ КОММУНИКАЦИИ В ЦИФРОВУЮ ЭПОХУ: ВЛИЯНИЕ ИНТЕРНЕТ-СРЕДЫ НА РУССКИЙ ЯЗЫК

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Abstract

The article examins how modern digital technologies and the Internet change common communication and influence the Russian language. It describes the characteristics of the new «digital generation», their online habies, and the formation of a special Internet language that combines features of spoken and written speech.

The paper analyzes the main changes in the vocabulary: the emergence of slang and Internet memes, shifts in the meanings of existing Russian words, and a large influx of loanwords.

Particular attention is paid to how these changes affect the methodology of teaching Russian as a Foreign Language (RFL). This direction is highly important for Armenia, where the Russian language remains in demand and is used for professional communication. It is concluded that digital borrowings and new speech formats are a natural process of language evolution that one needs to adapt to.

Аннотация

В статье рассматривается, как современные цифровые технологии и интернет меняют привычное общение и влияют на русский язык. В работе описаны особенности нового «цифрового поколения», его привычки в сети и формирование особого интернет-языка, который совмещает в себе черты устной и письменной речи.

Анализируются главные изменения в лексике: появление сленга, интернет-мемов, изменение значений уже существующих русских слов, а также большой поток заимствований.

Особое внимание уделяется тому, как эти изменения влияют на методику преподавания РКИ. Это направление очень важно для Армении, где русский языке востребован и используется для профессионального общения. Делается вывод о том, что цифровые заимствования и новые форматы речи - это естественный процесс развития языка, к которому нужно уметь адаптироваться.

Keywords: *Digital reality, Digital environment, Media texts, Digital generation, Internet language, Digitalization, Online discourse, Spontaneous writing, Anglicisms, Internet slang.*

Ключевые слова: *Цифровая реальность, цифровая среда, медиатексты, цифровое поколение, интернет-язык, цифровизация, сетевой дискурс, спонтанное письмо, англицизмы, интернет-сленг.*

ВВЕДЕНИЕ

Стремительное развитие цифровых технологий и широкое распространение интернет-коммуникации привели к существенным изменениям в жизни современного общества. Интернет стал не только источником информации, но и пространством для обучения, творчества и общения. Вместе с изменением коммуникативных практик трансформируется и язык, выступающий главным инструментом взаимодействия людей.

Особенно заметно влияние цифровой среды на русский язык, который активно пополняется новыми словами, изменяет существующие значения и вырабатывает новые формы речевого поведения. Интернет-коммуникация формирует особый тип дискурса,

сочетающий черты устной и письменной речи, а также способствует появлению новых способов выражения эмоций и передачи информации. В связи с этим исследование трансформации русского языка под воздействием цифровой среды представляет значительный научный интерес.

ЦИФРОВАЯ СРЕДА И ФОРМИРОВАНИЕ НОВОГО ПОКОЛЕНИЯ ПОЛЬЗОВАТЕЛЕЙ

Цифровая реальность открыла для нового поколения такие возможности, о которых раньше можно было только мечтать. Теперь не обязательно куда-то ехать, чтобы учиться или развиваться - достаточно интернета. Можно проходить обучение у специалистов из других стран, работать на расстоянии и самому решать, где жить и чем заниматься.

Цифровая среда предоставила новому поколению множество возможностей. Сегодня можно учиться дистанционно, осваивать новые навыки через видео и онлайн-курсы, работать из любой точки мира и самостоятельно выбирать удобный ритм жизни. Многие находят себя в творчестве, блогинге или интернет-проектах, используя технологии как способ самовыражения и заработка. Благодаря сети стало проще находить людей с похожими интересами, делиться опытом и получать поддержку. Американский психолог Шерри Постник-Гудвин так раскрывает детей «цифрового поколения»: «Они предпочтут текстовое сообщение разговору. Они общаются в сети – часто с друзьями, с которыми никогда не виделись. Они редко бывают на улице, если только родители не организуют их досуг. Они не представляют себе жизни без мобильных телефонов. Они никогда не видели мира, в котором не было высоких технологий или терроризма. Компьютеры они предпочитают книгам и во всём стремятся к немедленным результатам. Они выросли в эпоху экономической депрессии, и от них всеми ожидается лишь одно – быть успешными. Большинство из них очень быстро взрослеют, ведя себя значительно старше своих лет» [4]. Американский психолог Шерри Постник-Гудвин описывает детей современного цифрового поколения как особую категорию молодежи, чьи привычки, мировоззрение и стиль жизни сильно отличаются от предыдущих поколений. Эти дети привыкли к технологии с самого раннего возраста и воспринимают её как естественную часть своей повседневной жизни. Большинство представителей этого поколения не склонны проводить много времени на улице или заниматься активными играми, если только это не организовано родителями. Их жизнь практически невозможно представить без мобильных устройств и постоянного доступа к сети. Таким образом, наблюдения Постник-Гудвин показывают, что цифровое поколение - это не просто дети, привыкшие к гаджетам. Это целая когорта, чьи привычки, ценности и образ жизни отражают слияние технологической среды, социальных изменений и экономических вызовов, что делает их взросление быстрым и одновременно уникально адаптированным к современному миру. Они учатся жить в условиях постоянной информации, высокой скорости жизни и давления ожиданий, что формирует у них особую зрелость, но также ставит перед ними новые психологические и социальные вызовы.

ТРАНСФОРМАЦИЯ КОММУНИКАТИВНОГО ПРОСТРАНСТВА В УСЛОВИЯХ ЦИФРОВИЗАЦИИ

Развитие цифровых технологий и стремительное расширение интернета заметно повлияли на то, как сегодня устроено коммуникативное пространство. За последние десятилетия привычные модели общения существенно изменились, поскольку виртуальная среда всё глубже входит в повседневную жизнь человека. Интернет, который раньше был лишь дополнительным источником информации, постепенно превратился в полноценное пространство, где происходит почти всё: обычное бытовое общение, профессиональные контакты, обучение, творчество и организация совместной деятельности. Поэтому язык как главное средство общения тоже начал меняться: трансформации затронули структуру современной русской речи, её функциональные разновидности и нормы употребления. Цифровые технологии играют важную роль в развитии образовательного процесса. Они способствуют повышению эффективности обучения студентов, обеспечивают персонализированный подход и улучшают качество образования. При этом вопросы цифрового неравенства, доступа к технологиям и подготовки учителей остаются актуальными [2].

Лексическая система русского языка в XXI веке переживает один из самых интенсивных периодов преобразований за всю свою историю. Если ранее развитие лексики определялось преимущественно внутренними потребностями общества, культурными процессами или научно-техническим прогрессом, то сегодня ключевым драйвером изменений стала цифровизация - стремительное внедрение цифровых технологий во все сферы жизни. Интернет, мобильные устройства, социальные сети, виртуальная коммуникация и автоматизация бытовых процессов не только создают новые реалии, требующие номинации, но и формируют

новую языковую культуру, в основе которой лежит постоянное расширение и обновление словарного состава.

Интернет-язык - это динамичная и эволюционирующая форма языковой коммуникации, появившаяся в результате активного взаимодействия людей в цифровой среде. Он характеризуется уникальными чертами, обусловленными спецификой интернет- общения, такими как скорость обмена информацией, отсутствие формальностей и повсеместная доступность общения [3].

Цифровая среда формирует особый способ общения, где смешиваются черты устной и письменной речи. Чем активнее развиваются Интернет и его графические возможности, тем активнее появляются все новые знаки, символы, выражения, заменяющие определенные словосочетания, выражающие те или иные эмоции, отношение к сказанному [5]. Сообщения передаются быстро и спонтанно, при этом используются разные каналы - текст, изображения, видео, аудио, гиперссылки и мемы. Такой формат общения всё чаще называют гибридным или мультимодальным. В отличие от классической письменной речи, где важны аккуратность и завершённость, общение в интернете обычно фрагментарное, эмоционально насыщенное и ориентированное на живой диалог.

Одной из характерных черт онлайн-коммуникации становится её асинхронность, позволяющая общаться независимо от времени и места нахождения участников. В сочетании с технической лёгкостью создания сообщений это приводит к росту объёма письменной коммуникации. При этом многие её формы приобретают черты устной речи: они становятся более короткими, неполными по структуре, экономными и насыщенными эмоциональными маркерами, а также визуальными средствами, заменяющими невербальные сигналы.

Традиционная лингвистика долгое время чётко разделяла устную и письменную формы как два самостоятельных вида речевой деятельности. Однако с развитием интернет-общения эта граница постепенно размывается. Письменная коммуникация в сети всё чаще перенимает особенности разговорной речи: упрощённый синтаксис, преобладание коротких и простых предложений, использование неполных фраз, обилие междометий, звукоподражаний и графических маркеров.

Одной из ключевых характеристик становится спонтанное письмо - когда текст создаётся прямо в процессе общения и практически не редактируется. Из-за этого многие сообщения в цифровой среде напоминают устный монолог или диалог, что влияет на общую модель речевого поведения.

Цифровая эпоха привела к возникновению новых форм коммуникации, в которых сочетаются особенности устной и письменной речи. Интернет-дискурс становится самостоятельной формой языкового взаимодействия, обладающей собственными принципами организации и функционирования.

ОСОБЕННОСТИ ИНТЕРНЕТ-ДИСКУРСА И ЕГО ЗНАЧЕНИЕ ДЛЯ ПРЕПОДАВАНИЯ РУССКОГО ЯЗЫКА

Интернет также формирует особый тип дискурса, которому свойственны открытость и нелинейность. Пользователь в сети одновременно выступает и автором, и читателем, и комментатором. В отличие от традиционных форм коммуникации, online-дискурс создаётся коллективно: содержание формируется совместными усилиями, а границы между участниками и «владельцем» текста становятся размытыми.

Современная цифровая среда заметно влияет на способы общения, речевое поведение и даже на структуру самого языка. Для методики преподавания русского как иностранного (РКИ) это особенно важно, поскольку учащиеся сталкиваются не только с литературной нормой, но и с живой, быстро меняющейся речью, которая активно развивается в интернете. В Армении эта проблема становится ещё более значимой: русский язык здесь выполняет роль языка межнационального общения, остаётся востребованным среди молодёжи благодаря медиаплатформам и одновременно служит инструментом профессиональной коммуникации.

Цифровые изменения формируют новую реальность обучения: иностранный учащийся осваивает русский язык в условиях, когда словарный состав обновляется быстрее, чем успевают адаптироваться традиционные учебники. Особенно ярко это видно на примере интернет-лексики, англицизмов, медийных неологизмов и разнообразных гибридных языковых форм. Современный интернет-дискурс оказывает значительное влияние на практику преподавания русского языка. В условиях постоянного обновления языковых средств возникает

необходимость учитывать особенности цифровой коммуникации и адаптировать методические подходы к новым реалиям.

МОЛОДЁЖНЫЙ СЛЕНГ И МЕМЕТИЧЕСКАЯ КУЛЬТУРА В ЦИФРОВОЙ СРЕДЕ

Цифровая среда стала природной территорией формирования молодёжного жаргона, который затем проникает в широкий лексический оборот. Язык интернета динамичен, креативен, стремится к сокращению и экспрессии, поэтому сленговые слова легко закрепляются: кринж, рофл, шерить, вписка (в значение «совместный онлайн-проект»), диз, токсик, вайб, баз, чилл, эдвансед.

Особенность цифрового сленга - его меметичность. Многие слова существуют только в рамках конкретных медийных сюжетов и исчезают так же быстро, как появляются: флексить, краш, шаут-аут, эщкере и др. Е. И. Гончарова писала - «Интернет-мем представляет собой полимодальный текст, сочетающий вербальные и визуальные элементы, что делает его ценным дидактическим материалом при обучении русскому языку как иностранному» [1]. Также Гончарова и Сидорова отмечали - «Интернет-мем представляет собой жанр интернет-коммуникации, который сочетает вербальные и визуальные элементы, обладая специфическими функциями, культурно-лингвистической спецификой и образовательным потенциалом для использования в обучении русскому языку как иностранному» [1]. В статье Е. И. Гончаровой и Е. Ю. Сидоровой интернет-мем рассматривается не только как сочетание текста и изображения, но и с точки зрения его коммуникативной, образовательной и культурной ценности.

В отличие от традиционного жаргона, интернет-сленг имеет нестабильные, плавающие семантические поля, быстро изменяет значения, порождает многочисленные дериваты и модификации.

Цифровизация приводит к тому, что многие «старые» русские слова приобретают новые значения: друг - не только социально значимая фигура, но и «подписчик»; стена - элемент интерфейса; пост - публикация в сети; сообщество - группа пользователей; активность - степень реакции аудитории; модератор - не только регулирующий встречи человек, но и контролирующий правила онлайн-площадки. Такие процессы усложняют семантическую структуру языка и создают дополнительные слои значений, характерные именно для цифровой эпохи.

Интернет-сленг и мемы стали важной частью современной языковой культуры. Их высокая динамичность отражает процессы языкового творчества и демонстрирует тесную связь языка с цифровой культурой и медиапространством.

ПРОБЛЕМА ЯЗЫКОВЫХ ЗАИМСТВОВАНИЙ И ПЕРСПЕКТИВЫ РАЗВИТИЯ РУССКОГО ЯЗЫКА

Наиболее ярким проявлением влияния цифровой среды на лексику стал беспрецедентный рост заимствований из английского языка. Это связано с глобальным доминированием англоязычной IT-индустрии, отсутствием русских терминов для обозначения новых явлений, а также с высокой скоростью распространения информации в сети, когда новые слова практически мгновенно входят в повседневную речь. Активное проникновение англицизмов вызывает в обществе различные эмоции. Сторонники языкового развития считают заимствования естественным и необходимым процессом эволюции языка, тогда как критики видят в этом «засорение» русского языка иностранными словами.

Среди цифровых заимствований последних лет можно выделить несколько основных групп:

*а) **Технические и IT-термины:** апдейт, апгрейд, аккаунт, интерфейс, контент, хостинг, фейл, фолловер, блог, пост, стрим, стример, фриланс, бренд, стартап, софт, девелопер, таргет, куратор контента, нейросеть и др.*

Большинство этих слов либо не имеют точных русских аналогов, либо соответствующие варианты длиннее и менее удобны для использования.

*б) **Социально-медийные понятия:** лайк, дизлайк, репост, шэр, сторис, хайлайты, тред, мем, хэштег, аватар, никнейм, юзер, чат, батл, фандом.*

Эти термины активно употребляются в молодёжной и повседневной речи и постепенно становятся общеупотребительными.

*в) **Экономические и профессиональные термины цифровой сферы:** краудфандинг, копирайтер, маркетплейс, мерч, логист, продакт-менеджер, комьюнити-менеджер, инфлюенсер.*

Многие из этих слов уже закрепились в профессиональных стандартах и официальных документах, что свидетельствует о их легитимации в современном языке.

В рамках сетевого дискурса постепенно складывается особый интернет-язык - подвижная, постоянно обновляющаяся подсистема русского, которая меняется почти ежедневно. Для него характерны несколько ярких особенностей.

1. Сетевой жаргон и сленг. Он включает различные аббревиатуры и сокращения: лмд, лол, омг, имхо, крч. Широко распространены и намеренные искажения слов: нить (вместо «не идти» как мем), кек, мяу, пж, спс. К этому же относятся устойчивые меметические фразы, например: «я устал, я ухожу», «это фиаско, братан», «а можно без этого?».

2. Транслитерация и смешение алфавитов. Пользователи активно пишут русские слова латиницей: privet, kak dela, poka, ok, а иногда даже смешивают кириллицу и латиницу в одном слове: kruto, spasibo, okeушн.

3. Графические способы выражения эмоций. Коммуникацию оживляют эмодзи, смайлы и стикеры: также символические конструкции вроде ^^, :3, ¯_(ツ)_/¯. Они выполняют роль заменителей интонации и мимики.

4. Упрощённый синтаксис. Фразы становятся короче и разговорнее: «ща буду», «я норм», «не понял», «такое себе», «пойду посплю». Это делает письменную речь ближе к устной.

5. Хэштеги как функциональная единица. Хэштеги выполняют сразу несколько задач: маркируют тему, задают тон высказыванию, структурируют поток сообщений: #настроение, #работаю, #жизньболь, #шутка.

6. Мемы как культурные и языковые маркеры. Мемы передают сложный контекст в нескольких словах или картинке: «пока-пока» с пингвином, «кот, которому всё надоело», «драматический хомяк». Нередко одно изображение становится полноценной репликой в диалоге.

Главные аргументы критиков заключаются в том, что заимствования вытесняют традиционную лексику, при этом нарушаются принципы русской словообразовательной системы. Все это ведет к искажению культурной идентичности, а удобство и краткость заменяют смысловую точность. Однако лингвистическая практика показывает, что язык самостоятельно отбирает только те слова, которые действительно нужны обществу. В истории русского языка были десятки волн заимствований - французских, немецких, голландских - и все они в итоге гармонично встроились в систему, не разрушив её.

Именно поэтому большинство современных исследователей придерживается позиции умеренного языкового либерализма: цифровые заимствования не угрожают языку, если проходят полноценную адаптацию и используются в соответствующих сферах.

Несмотря на существующие опасения относительно чрезмерного влияния иностранных слов, развитие русского языка свидетельствует о его способности органично адаптировать новые элементы. Языковая система сохраняет устойчивость и самостоятельно регулирует процессы лексического обновления.

ЗАКЛЮЧЕНИЕ

Развитие цифровых технологий и распространение интернет-коммуникации оказывают комплексное влияние на русский язык. Изменения затрагивают не только словарный состав, но и особенности речевого поведения, способы выражения эмоций, формы коммуникации и принципы организации дискурса. Интернет-пространство способствует возникновению новых лексических единиц, активному проникновению англицизмов, развитию молодёжного сленга и формированию гибридных форм общения, объединяющих признаки устной и письменной речи.

Несмотря на высокую динамичность языковых процессов, современный русский язык сохраняет способность к адаптации и дальнейшему развитию. Цифровая среда не разрушает языковую систему, а становится важным фактором её эволюции, отражая изменения, происходящие в обществе, культуре и коммуникации XXI века.

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RETURNING HOME BUT NOT BELONGING: LANGUAGE POLICY AND THE EDUCATIONAL EXPERIENCES OF ETHNIC KAZAKH RETURN MIGRANTS

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Abstract

Since independence, Kazakhstan has pursued an active policy of ethnic return migration, encouraging members of the Kazakh diaspora to resettle in their historical homeland. Although these return migrants, officially known as Qandas, are expected to strengthen national identity and demographic development, their integration into educational institutions remains challenging. This article critically examines how language policy influences the educational experiences of ethnic Kazakh return migrants in Kazakhstan. Drawing upon literature on ethnic return migration, language policy, and educational inclusion, the paper explores the paradox of belonging experienced by return migrants who are ethnically Kazakh yet frequently encounter linguistic, cultural, and institutional barriers. The analysis demonstrates that Kazakhstan's multilingual language policy, while promoting Kazakh, Russian, and English, often reproduces inequalities for students whose educational and linguistic backgrounds differ from mainstream expectations. The article argues that language functions not only as a medium of communication but also as a form of symbolic capital that shapes access to educational opportunities and social acceptance. The study contributes to broader discussions on migration, language policy, and educational equity in multilingual societies and offers recommendations for developing more inclusive educational practices for return migrant students.

Keywords: *Qandas, oralman, ethnic return migration, language policy, educational experiences, Kazakhstan, belonging, educational inclusion*

Introduction

The collapse of the Soviet Union created new opportunities for nation-building across Central Asia. In Kazakhstan, one of the most significant nation-building initiatives was the implementation of a large-scale ethnic repatriation program designed to encourage members of the global Kazakh diaspora to return to their ancestral homeland. Since 1991, nearly one million ethnic Kazakhs have migrated to Kazakhstan from neighboring countries including Mongolia, China, Uzbekistan, Turkmenistan, Afghanistan, and Iran. Initially referred to as Oralman and later officially renamed Qandas, these migrants have occupied a unique position within Kazakhstani society.

The repatriation policy was developed as part of a broader national strategy aimed at strengthening the demographic position of ethnic Kazakhs, restoring historical justice, and reinforcing national identity after decades of Soviet influence. Government discourse often presents return migrants as individuals who have preserved authentic Kazakh language, traditions, and cultural practices while living outside the borders of Kazakhstan. Consequently, their return is frequently portrayed as a symbolic restoration of the nation.

However, scholarly research increasingly demonstrates that ethnic belonging does not automatically guarantee social inclusion. Despite sharing a common ethnic identity with the majority population, many return migrants experience significant difficulties integrating into Kazakhstani society. Werner, Emmelhainz, and Barcus (2017) describe this phenomenon as "privileged exclusion," a condition in which return migrants simultaneously possess symbolic advantages associated with ethnic membership while facing exclusion from social, political, and educational structures. Their research highlights a paradox: individuals who return "home" often discover that the homeland is socially and culturally different from the imagined community they expected to join.

One of the most important yet understudied dimensions of this paradox is education. Schools and universities constitute key sites of socialization, language acquisition, and identity formation. For return migrant children and youth, educational institutions frequently represent the first point of sustained interaction with mainstream Kazakhstani society. Success within these institutions influences not only academic outcomes but also broader processes of integration, social mobility, and belonging.

Language occupies a central role in these experiences. Kazakhstan officially promotes a multilingual language policy based on the development of Kazakh, Russian, and English. Since independence, substantial efforts have been made to strengthen the status of Kazakh as the state language while maintaining Russian as a language of interethnic communication and expanding English as a language of global competitiveness. Although this policy reflects the country's multicultural aspirations, it also creates complex challenges for return migrant students.

Many ethnic Kazakh return migrants arrive with linguistic repertoires that differ significantly from those expected within Kazakhstan's educational system. Students from Mongolia often possess strong oral and written Kazakh skills but limited knowledge of Russian. Those arriving from China may use Arabic-based or Latin-based scripts rather than Cyrillic. Others have developed educational competencies within entirely different linguistic systems. As a result, educational adaptation frequently involves learning not only new curricula but also new languages, scripts, and communicative norms.

Research suggests that Russian remains particularly significant in shaping educational opportunities despite policies promoting Kazakh-language education. Zhilbayev (2018) notes that many oralman children encounter difficulties due to insufficient Russian language proficiency, which limits access to educational resources and social networks. Similar findings are reported in studies of university students from Mongolia and China, where language barriers contribute to academic stress, reduced participation, and challenges in establishing social relationships.

The educational experiences of return migrants also reveal broader tensions within Kazakhstan's nation-building project. On one hand, state policies encourage ethnic return migration as a mechanism for strengthening Kazakh identity. On the other hand, institutional structures often privilege linguistic and cultural competencies associated with Soviet and post-Soviet socialization. Consequently, return migrants may find themselves positioned as ethnic insiders but social outsiders. This contradiction challenges assumptions that shared ethnicity naturally leads to successful integration.

The concept of belonging provides an important analytical framework for understanding these experiences. Belonging extends beyond legal citizenship or ethnic identity and encompasses emotional attachment, social recognition, and participation in everyday life. Educational institutions play a critical role in producing or denying such belonging. Students who are unable to access dominant linguistic practices may experience exclusion even when formal policies emphasize inclusion. Therefore, examining educational experiences offers valuable insight into how national identity is negotiated in practice.

Despite growing scholarship on ethnic return migration in Kazakhstan, relatively limited attention has been devoted to the intersection of language policy and education. Existing studies tend to focus on citizenship, labor market integration, demographic policy, or cultural adaptation. While these issues are undoubtedly important, the educational dimension remains insufficiently explored. Moreover, few studies systematically connect educational challenges to broader language policy frameworks and theories of belonging.

This article addresses this gap by critically reviewing existing literature on ethnic Kazakh return migrants and examining how language policy shapes their educational experiences. Specifically, the study seeks to answer three research questions:

1. *How does Kazakhstan's language policy influence the educational experiences of ethnic Kazakh return migrants?*
2. *What linguistic barriers affect the educational integration of return migrant students?*
3. *How do educational institutions contribute to experiences of belonging and exclusion among return migrants?*

By addressing these questions, the article contributes to discussions on migration, multilingualism, and educational equity in post-Soviet societies. It also provides insights for policymakers seeking to create more inclusive educational environments for diverse student populations. Ultimately, the experiences of ethnic Kazakh return migrants demonstrate that returning home does not necessarily guarantee belonging. Instead, belonging must be continuously negotiated through language, education, and everyday social interactions.

Literature Review

Ethnic Return Migration: Conceptualizing Return and Belonging

Ethnic return migration refers to the movement of individuals who migrate to a state that they perceive as their ancestral homeland based on shared ethnic, cultural, linguistic, or historical ties. Unlike conventional forms of migration, ethnic return migration is often framed by governments and societies as a process of "coming home." However, scholars increasingly argue that return migration is not simply

a geographical movement but a complex social process involving negotiations of identity, citizenship, belonging, and inclusion.

Much of the literature on ethnic return migration challenges the assumption that ethnic affinity automatically facilitates integration. Tsuda (2009) argues that return migrants frequently discover a discrepancy between symbolic membership in the nation and actual social acceptance. While they may be legally welcomed as members of the ethnic majority, they often encounter social exclusion due to differences in language, education, cultural practices, and everyday behavior. Consequently, ethnic return migrants frequently occupy an ambiguous position situated between insider and outsider status.

This tension is particularly visible in post-socialist states where nation-building projects actively encourage diaspora return. Such policies are often motivated by demographic concerns, historical narratives of national restoration, and efforts to strengthen ethnic majorities. Yet the implementation of these policies frequently reveals contradictions between symbolic inclusion and practical integration. Return migrants may be celebrated in official discourse while simultaneously encountering institutional barriers in education, employment, and social life.

Kazakhstan provides a compelling case for examining these contradictions. Since independence, the government has actively promoted the repatriation of ethnic Kazakhs from neighboring countries and distant diaspora communities. Official narratives frequently describe return migrants as individuals who preserved authentic Kazakh traditions and language during periods of foreign domination. Within this discourse, return migration is represented not merely as migration but as a moral and historical restoration of the nation.

However, empirical evidence suggests that the lived experiences of return migrants often differ substantially from official expectations. Rather than experiencing immediate acceptance, many migrants report challenges associated with linguistic differences, cultural misunderstandings, bureaucratic obstacles, and limited social networks. These experiences demonstrate that ethnic identity alone is insufficient to guarantee belonging within contemporary Kazakhstan.

Privileged Exclusion and the Paradox of Returning Home

One of the most influential contributions to the study of return migration in Kazakhstan is the concept of "privileged exclusion" developed by Werner, Emmelhainz, and Barcus (2017). Their research highlights a fundamental paradox within Kazakhstan's repatriation program. Ethnic Kazakh return migrants receive symbolic privileges because they belong to the titular ethnic group and contribute to state demographic goals. At the same time, they often experience exclusion from social and institutional structures that continue to privilege competencies associated with Soviet and post-Soviet socialization.

The concept of privileged exclusion challenges binary understandings of inclusion and exclusion. Instead of being fully accepted or fully marginalized, return migrants simultaneously occupy both positions. Their ethnic identity grants them access to legal recognition and state support, yet differences in language, educational background, and cultural experience frequently limit their participation in mainstream society.

For many return migrants, the most significant source of exclusion is language. Although they are ethnic Kazakhs, their linguistic repertoires often differ from those of local populations. Kazakhs arriving from Mongolia, for example, may speak fluent Kazakh but possess limited Russian proficiency. Others may use different alphabets, educational terminologies, or linguistic norms. These differences create barriers within institutions where Russian continues to function as an important language of communication and administration.

The notion of belonging is particularly relevant to understanding these dynamics. Belonging is not merely a legal status but a social process through which individuals are recognized as legitimate members of a community. Yuval-Davis (2011) argues that belonging operates through emotional attachment, social participation, and political recognition. Educational institutions represent one of the primary sites where belonging is constructed and contested because they shape opportunities for participation, achievement, and social interaction.

In the context of Kazakhstan, return migrants often possess formal membership within the national community but struggle to achieve social recognition. Their experiences suggest that belonging is not determined solely by ethnicity but is deeply influenced by language practices and institutional expectations.

Language Policy in Kazakhstan: Historical Development and Contemporary Challenges

Language policy has occupied a central position in Kazakhstan's nation-building strategy since independence. Following the dissolution of the Soviet Union, policymakers faced the challenge of strengthening Kazakh national identity while maintaining social stability within a multilingual society.

The Constitution of Kazakhstan recognizes Kazakh as the state language while granting Russian official status in public administration and interethnic communication. Over time, educational reforms have increasingly promoted the development of Kazakh-language education and expanded opportunities for learning English. This policy evolved into the widely discussed trilingual model that emphasizes proficiency in Kazakh, Russian, and English.

Supporters of trilingual education argue that it enables Kazakhstan to balance national identity, regional communication, and global competitiveness. Kazakh strengthens cultural heritage and national cohesion, Russian facilitates communication across the post-Soviet space, and English provides access to international knowledge and economic opportunities.

Despite these objectives, scholars have identified tensions within the implementation of language policy. While Kazakh has gained prominence in public discourse, Russian continues to possess substantial symbolic and practical value. Russian remains widely used in higher education, scientific communication, professional environments, and urban social life. Consequently, proficiency in Russian often functions as a form of linguistic capital that influences access to opportunities.

Drawing upon Bourdieu's theory of linguistic capital, language can be understood not merely as a communication tool but as a resource that carries social and economic value. Individuals possessing dominant linguistic competencies gain advantages within educational and professional fields, while those lacking such competencies may experience exclusion. In Kazakhstan, Russian frequently operates as such a resource despite official efforts to elevate the status of Kazakh.

This situation creates challenges for return migrant students. Although many arrive with strong Kazakh-language skills, they may lack proficiency in Russian or familiarity with educational practices shaped by Soviet traditions. As a result, they encounter barriers that are often invisible within official narratives of national unity.

Educational Experiences of Ethnic Kazakh Return Migrants

Education represents one of the most important arenas through which return migrants engage with Kazakhstani society. Schools and universities not only provide academic knowledge but also facilitate social integration, language acquisition, and identity development. Consequently, educational experiences significantly influence broader processes of adaptation and belonging.

Research consistently identifies language as a primary challenge for return migrant students. Zhilbayev (2018) reports that oralman children frequently encounter difficulties associated with limited Russian proficiency and unfamiliarity with Cyrillic literacy practices. These challenges affect academic performance, classroom participation, and communication with peers and teachers.

Students arriving from Mongolia, China, and other countries often possess educational backgrounds shaped by different curricula and linguistic environments. While some demonstrate strong oral competence in Kazakh, they may struggle with academic terminology, written communication, or multilingual instruction. Others face difficulties adjusting to educational expectations that differ substantially from those in their countries of origin.

Recent studies have further highlighted the experiences of university students. Research on students from Mongolia and China demonstrates that linguistic barriers extend beyond the classroom and influence social integration. Limited proficiency in dominant languages may restrict participation in student organizations, informal peer networks, and extracurricular activities. Consequently, educational challenges become intertwined with broader experiences of isolation and exclusion.

The role of family has also emerged as an important factor in educational adaptation. Studies indicate that family networks often provide emotional support, practical assistance, and cultural continuity during the integration process. However, parents themselves may experience difficulties navigating educational institutions, particularly when they are unfamiliar with local administrative procedures or literacy conventions.

Another recurring theme in the literature concerns the discrepancy between expectations and reality. Many return migrants arrive with idealized perceptions of the homeland based on cultural narratives transmitted through diaspora communities. Educational institutions are often expected to facilitate integration and reinforce a sense of national belonging. Instead, some students encounter environments in which linguistic and cultural differences become sources of marginalization.

These experiences reveal that educational integration involves more than academic adjustment. It also requires navigating complex social hierarchies shaped by language, culture, and historical experience. Therefore, educational outcomes cannot be understood independently of broader social and political contexts.

Research Gap

Although scholarship on ethnic return migration in Kazakhstan has expanded considerably over the past decade, several important gaps remain. First, much of the existing literature focuses on citizenship, demographic policy, labor market participation, or cultural adaptation. Comparatively less attention has been devoted to educational experiences as a distinct area of analysis.

Second, studies examining educational integration often treat language barriers as individual challenges rather than structural consequences of language policy. As a result, insufficient attention has been paid to the relationship between multilingual educational reforms and the experiences of return migrant students.

Third, relatively few studies explicitly connect language policy, educational inclusion, and belonging within a single analytical framework. Existing research frequently discusses these themes separately despite their close interrelationship in the everyday lives of return migrants.

Finally, recent policy developments, including the transition from the term "oralman" to "qandas" and ongoing reforms in multilingual education, have created new contexts that require further scholarly examination. Understanding how these changes affect educational experiences remains an important task for future research.

Addressing these gaps is essential for developing a more comprehensive understanding of return migration in Kazakhstan. Examining educational experiences through the lens of language policy and belonging can provide valuable insights into the mechanisms through which inclusion and exclusion are produced within contemporary nation-building processes.

Theoretical Framework

This article draws upon three complementary theoretical perspectives: Bourdieu's concept of linguistic capital, Spolsky's language policy framework, and Yuval-Davis's theory of belonging. Together, these perspectives provide a comprehensive analytical lens for understanding how language policy shapes the educational experiences of ethnic Kazakh return migrants in Kazakhstan.

Linguistic Capital and Educational Inequality

Pierre Bourdieu's theory of linguistic capital provides a useful framework for understanding the relationship between language and social power. According to Bourdieu (1991), language is not merely a neutral means of communication. Rather, particular languages and language varieties possess different values within specific social contexts. Individuals who command socially valued languages gain access to educational, economic, and social opportunities, while those who lack such competencies may experience disadvantage.

Within educational institutions, linguistic capital functions as a mechanism through which inequalities are reproduced. Schools and universities often reward students who possess dominant linguistic competencies while unintentionally marginalizing those whose linguistic backgrounds differ from institutional expectations. As a result, language becomes a form of symbolic power that shapes educational trajectories and life chances.

In the context of Kazakhstan, linguistic capital is distributed unevenly across different languages. Although Kazakh has acquired increasing political significance as the state language, Russian continues to occupy an influential position within education, professional communication, and urban social life. English has also emerged as a valuable resource associated with globalization and academic mobility. Consequently, students who possess competence in all three languages generally enjoy greater educational advantages.

For ethnic Kazakh return migrants, this linguistic hierarchy can create significant challenges. Many return migrants arrive with strong Kazakh-language skills but limited proficiency in Russian or English. While their knowledge of Kazakh may align with state narratives of national identity, it does not necessarily translate into educational success within multilingual institutions. Thus, linguistic capital provides an important explanation for why ethnic belonging does not automatically result in educational inclusion.

Language Policy as Practice

To understand how these inequalities emerge, the article employs Spolsky's (2004) language policy framework. Spolsky conceptualizes language policy as consisting of three interconnected components: language practices, language beliefs or ideologies, and language management.

Language practices refer to the actual languages used in everyday interactions. Language beliefs encompass societal attitudes regarding the value and status of different languages. Language management includes official policies and regulations designed to influence language use.

This framework is particularly relevant to Kazakhstan because the country's language situation is characterized by a complex interaction between official policy and everyday practice. Official discourse promotes Kazakh as the state language and emphasizes the importance of multilingualism. However, actual language practices often reveal a more complicated reality in which Russian continues to function as a dominant language in many educational and professional settings.

For return migrant students, the distinction between policy and practice is especially significant. Officially, their knowledge of Kazakh should facilitate integration into educational institutions. In practice, however, successful participation often requires competence in Russian and increasingly in English. As a result, students may encounter barriers that are not immediately visible within formal policy documents.

Spolsky's framework therefore enables a critical examination of how language policies operate beyond official declarations and how educational institutions become sites where broader ideological and political tensions are reproduced.

Belonging as a Social Process

While linguistic capital and language policy explain structural inequalities, they do not fully capture the emotional and social dimensions of return migration. To address this limitation, the article incorporates Yuval-Davis's (2011) theory of belonging.

Yuval-Davis argues that belonging should be understood as a dynamic social process rather than a fixed identity category. Belonging involves emotional attachment, social participation, and recognition by others. Individuals may legally belong to a nation while simultaneously feeling excluded from its social and cultural life.

The theory is particularly useful for analyzing ethnic return migration because return migrants often possess formal membership in the national community but continue to experience exclusion. Their ethnic identity may be recognized by the state, yet their everyday interactions can challenge their sense of acceptance and inclusion.

Educational institutions play a central role in shaping experiences of belonging. Schools and universities are not only sites of learning but also spaces where students develop friendships, construct identities, and negotiate social membership. Positive educational experiences can strengthen feelings of belonging, while exclusionary practices may reinforce perceptions of marginalization.

For ethnic Kazakh return migrants, belonging is often negotiated through language. Students who are unable to participate fully in classroom discussions, communicate effectively with peers, or access educational resources may experience a weakened sense of connection to the broader community. Consequently, language becomes both a practical and symbolic dimension of belonging.

Integrated Analytical Framework

The combination of these three theoretical perspectives allows for a multidimensional analysis of return migrant educational experiences.

Bourdieu's concept of linguistic capital explains how language competencies function as valuable resources that shape educational opportunities. Spolsky's framework reveals how language policies and practices create institutional conditions that privilege certain linguistic repertoires over others. Yuval-Davis's theory of belonging highlights the social and emotional consequences of these processes for return migrant students.

Together, these perspectives suggest that educational challenges experienced by ethnic Kazakh return migrants cannot be reduced to individual linguistic deficiencies. Instead, they emerge from the interaction between institutional language policies, unequal distributions of linguistic capital, and broader processes of social recognition and belonging.

This integrated framework forms the basis for the discussion presented in the following section, which critically examines how language policy contributes to both inclusion and exclusion within Kazakhstan's educational system.

Discussion

The literature reviewed in this article reveals a fundamental contradiction within Kazakhstan's ethnic repatriation and language policies. While ethnic Kazakh return migrants are symbolically positioned as members of the national community, their educational experiences often reflect various forms of exclusion. This contradiction demonstrates that belonging is not determined solely by ethnicity but is shaped through language, institutional practices, and everyday social interactions. The findings of previous studies suggest that educational institutions serve as critical spaces where these tensions become visible.

Russian as the Hidden Gatekeeper of Educational Success

One of the most significant themes emerging from the literature is the continued importance of Russian within Kazakhstan's educational system. Although state policy has increasingly emphasized the promotion of Kazakh and the development of multilingual education, Russian remains deeply embedded in academic, professional, and social life.

This situation creates what may be described as a hidden gatekeeping mechanism. Officially, Kazakhstan promotes inclusion through recognition of ethnic Kazakhs regardless of their country of origin. However, practical success within educational institutions frequently depends upon competencies that many return migrants do not possess upon arrival. In particular, limited proficiency in Russian often restricts access to academic materials, communication with peers, and participation in institutional life.

From the perspective of Bourdieu's theory, Russian continues to function as a powerful form of linguistic capital. Students who possess Russian-language proficiency gain access to educational resources and social networks that facilitate academic success. Conversely, return migrant students who primarily speak Kazakh may encounter disadvantages despite belonging to the titular ethnic group.

This finding highlights an important tension within Kazakhstan's nation-building project. While the state seeks to strengthen the role of Kazakh, institutional practices often continue to reward competencies associated with Russian. As a result, educational inclusion may depend less on ethnic identity than on access to dominant linguistic resources.

The experiences of return migrants therefore challenge simplistic assumptions regarding language revitalization and national integration. The promotion of Kazakh alone does not eliminate existing linguistic hierarchies. Instead, multiple languages continue to occupy different positions within educational and social structures, creating unequal opportunities for students from diverse backgrounds.

The Paradox of Ethnic Inclusion and Linguistic Exclusion

The literature consistently demonstrates that return migrants experience a paradoxical form of integration. On one hand, they are welcomed as ethnic Kazakhs returning to their ancestral homeland. On the other hand, they often encounter barriers associated with language, culture, and educational background.

This paradox can be understood through the concept of privileged exclusion. Return migrants possess symbolic advantages because they contribute to state demographic goals and reinforce narratives of national unity. Their return is frequently celebrated as evidence of the success of Kazakhstan's repatriation policies. However, symbolic inclusion does not necessarily translate into practical equality.

Language plays a central role in this contradiction. Many return migrants arrive with strong commitments to Kazakh culture and identity. Some possess linguistic skills that are even regarded as more "traditional" or "authentic" than those of local populations. Nevertheless, these competencies do not always align with the linguistic expectations of contemporary educational institutions.

Students from Mongolia, China, and other countries often discover that successful participation requires familiarity with Russian terminology, Soviet-influenced educational norms, and local communicative practices. Consequently, they may feel culturally connected to Kazakhstan while simultaneously experiencing educational exclusion.

This phenomenon demonstrates that language functions as more than a communication tool. It also serves as a marker of legitimacy and social membership. Individuals who possess dominant linguistic competencies are more likely to be recognized as fully belonging members of the educational community. Those lacking such competencies may experience subtle forms of marginalization despite their ethnic status.

The paradox of ethnic inclusion and linguistic exclusion reveals broader complexities within contemporary nation-building processes. Shared ancestry alone cannot eliminate structural inequalities created through language policy and institutional practice.

Educational Institutions as Sites of Belonging and Othering

The reviewed studies suggest that educational institutions play a dual role in the lives of return migrant students. On one hand, schools and universities provide opportunities for language acquisition, social integration, and academic advancement. On the other hand, they may also reproduce mechanisms of exclusion and othering.

Educational environments shape belonging through everyday interactions. Classroom participation, peer relationships, teacher expectations, and institutional support all influence whether students perceive themselves as accepted members of the educational community. For return migrants, these experiences are particularly important because education often represents their primary point of contact with mainstream society.

Research indicates that language barriers can affect not only academic performance but also social participation. Students who struggle to communicate effectively may avoid classroom discussions, experience difficulties forming friendships, and become less involved in extracurricular activities. Over time, these challenges can contribute to feelings of isolation and reduced self-confidence.

The concept of othering is useful for understanding these processes. Othering occurs when individuals are perceived as different from a socially constructed norm and are consequently positioned outside the boundaries of full membership. Although return migrants are ethnically Kazakh, differences in accent, vocabulary, educational background, or cultural practices may cause them to be perceived as outsiders.

This form of exclusion is often subtle rather than overt. Students may not experience direct discrimination, yet they may encounter assumptions regarding their abilities, backgrounds, or identities. Such experiences can weaken their sense of belonging and complicate their adaptation to educational environments.

At the same time, educational institutions possess significant potential to promote inclusion. Supportive teachers, language assistance programs, mentoring initiatives, and culturally responsive curricula can help facilitate successful integration. Therefore, schools and universities should be viewed not merely as sites where exclusion occurs but also as institutions capable of reducing educational inequalities.

Implications for Language Policy and Educational Equity

The experiences of ethnic Kazakh return migrants raise important questions regarding the relationship between language policy and educational equity in Kazakhstan. Existing policies have made significant progress in strengthening the status of Kazakh and expanding multilingual education. However, the literature suggests that additional measures are necessary to address the specific needs of return migrant students.

First, policymakers should recognize that return migrants constitute a linguistically diverse population rather than a homogeneous group. Students arrive from different countries with varying educational histories, literacy practices, and language competencies. Consequently, uniform integration strategies may fail to address their specific challenges.

Second, educational institutions should develop targeted language support programs that extend beyond basic language instruction. Such programs should assist students in acquiring academic literacy, disciplinary vocabulary, and communicative competencies necessary for successful participation in educational settings.

Third, greater attention should be devoted to teacher preparation. Educators require training that enables them to work effectively with linguistically and culturally diverse students. Awareness of return migrant experiences can help teachers create more inclusive classroom environments and avoid deficit-based interpretations of linguistic differences.

Fourth, educational policy should move beyond narrow measures of language proficiency and consider broader questions of belonging and participation. Successful integration should not be evaluated solely through academic achievement but also through indicators such as social inclusion, student well-being, and access to educational opportunities.

Finally, future language policy initiatives should acknowledge the gap that sometimes exists between official discourse and institutional practice. While multilingualism remains an important national objective, policymakers must ensure that language policies do not unintentionally reproduce inequalities for vulnerable student populations.

Taken together, these implications suggest that educational equity requires more than formal access to schooling. It demands institutional structures that recognize diversity, support linguistic adaptation, and foster meaningful belonging for all students, including ethnic return migrants.

Conclusion

This article examined the relationship between language policy and the educational experiences of ethnic Kazakh return migrants in Kazakhstan. Through a critical review of the literature, the study explored how language shapes educational integration, belonging, and access to opportunities within schools and universities.

The analysis demonstrates that ethnic return migrants occupy a unique and often contradictory position within Kazakhstani society. Although they are welcomed as members of the titular ethnic group and are viewed as contributors to national development, many continue to face educational challenges associated with language and institutional adaptation. These experiences illustrate that ethnic identity alone is insufficient to guarantee social inclusion.

Drawing on the concepts of linguistic capital, language policy, and belonging, the article argued that educational inequalities emerge through the interaction of individual competencies and institutional structures. Russian continues to function as a significant form of linguistic capital despite efforts to strengthen Kazakh-language education. Consequently, return migrant students who possess strong Kazakh-language skills but limited Russian proficiency may experience barriers that affect both academic success and social integration.

The findings also highlight the importance of understanding belonging as a social process rather than a fixed status. Educational institutions play a crucial role in shaping whether students feel accepted, recognized, and valued within the national community. For many return migrants, experiences of belonging are negotiated through language, participation, and everyday interactions.

Ultimately, the case of ethnic Kazakh return migrants reveals broader tensions within contemporary nation-building projects. The aspiration to unite members of a shared ethnic community may coexist with institutional practices that reproduce exclusion. Addressing these contradictions requires educational policies that move beyond symbolic inclusion and actively support equitable participation for diverse student populations.

Future research should continue to investigate the voices and experiences of return migrant students themselves. Qualitative studies involving interviews and ethnographic approaches could provide deeper insight into how language policy is experienced in everyday educational contexts. Such research would contribute not only to scholarship on Kazakhstan but also to wider discussions concerning migration, multilingualism, and educational justice in increasingly diverse societies.

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PECULIARITIES OF THE ADVERTISING DISCOURSE

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Abstract

Advertising has become one of the most influential forms of communication in modern society, serving as a bridge between producers and consumers while shaping public attitudes, preferences, and behavior. This article explores the concept of communication and examines the specific characteristics of advertising as one of its most vital and influential forms. The study's objectives are to examine how advertising has changed over time, from its earliest forms to its current ones, and to identify the key mechanisms through which advertising influences target audiences. The research demonstrates that advertising has evolved alongside human civilization and technological progress. The author traces the historical evolution of advertising, charting its transition from primitive visual symbols used in antiquity and the Middles Ages to today's dynamic, multi-channel marketing strategies. The paper analyzes the foundational functions of advertising – namely economic, informational, and social – and highlights information and communication as its core drivers. Furthermore, the study addresses the economic, informational, social, educational, cultural, and communication roles that advertising plays in modern society as well as it identifies three distinct types of communicative interaction within the advertising sphere: imitation, dialogue, and control. Particular attention is paid to how target audiences are segmented and how visual design, psychological appeal, and strategic language choices are utilized to ensure brand identity product memorability. The analysis reveals that in order to grab consumers' attention and leave a lasting impression, advertisers use persuasive language strategies, vivid imagery, metaphors, catchy slogans, and informal style. Finally, the article provides a comprehensive classification of modern advertising mediums, including outdoor, transit, print, and direct mail marketing, concluding that every format serves a specific objective, strategy, and purpose. The results show that although advertising styles and technologies have changed significantly, its basic goal of informing, persuading, and establishing effective communication with certain audiences has not altered. advertising is still a vital component of marketing and social communication, adjusting to the shifting demands of society while continuing to be a potent tool for persuasion and information sharing.

Keywords: *Communication, Advertising, Marketing, Advertising language, Target audience, Communicative interaction*

Introduction

The word «communication» originates from the Latin word, which means «to make common» or «to bind». In the modern understanding, communication is a process determined by social norms, during which information is transmitted and received. This process can take place both at the level of interpersonal interaction and on the scale of mass communication, using various channels and communication tools for this purpose. The search for a method to transform the individual exchange of ideas and information into a force capable of influencing public opinion and behavior is the essence of the communication dilemma. As Ph. Kotler notes, «Advertising is a non-personal form of communication carried out through paid means of information dissemination, with a clearly indicated source of funding» [2, p. 511].

By this, the author means that non-personal adverting is characterized by wide coverage, using a one-to-many approach instead of individual communication. The advantage of this approach is the ability to simultaneously deliver a single message to a huge audience, despite the lack of instant reaction inherent in personal scale.

The Historical Development of Advertising

Advertising as a type of activity is aimed at selling a product or service to target consumers. This is a kind of communication between the company and its customers. Advertising exists in all periods of our lives, and design and language are an important part of it.

The need to share facts or promote the quality of goods and services has increased the importance of advertising over the years. Nowadays, as a type of communication, advertising is a vital aspect of human life. Communication is carried out using language, which is the dominant means of advertising.

Marketing, of which advertising is a part, has reached a significant age and still remains a distinctive way of influencing people. The history of the advertising method describes the transition from

personal marketing messages to unnatural repetitive advertisements published in the first newspapers, to the dynamism of mass communication through radio and television, to the re-personalization of messages transmitted over cable, the Internet and direct communication. This is a story about sellers trying to find the best ways to attract customers, and a parallel narrative about how the world accepts them, how they resist, how they rejoice and how they are annoyed. Advertising has undergone changes, having reached the Golden Age of its development, and is currently the key to marketing success. It has evolved and gone through several significant periods of development that are closely related to the evolution of humanity [3, p.7].

Advertising has always existed ahead of people's awareness of it. The low level of education and sophistication of the population led to the use of signs, images and symbols as the primary early advertising mediums. The past, whether in antiquity or the Middle Ages, was characterized by the fact that reading was the privilege of a few – the clergy and the aristocracy. For the common man, writing, and therefore any text advertisement, was just a meaningless set of signs. To attract customers, merchants had to rely on a kind of «universal language». Today, this language has taken on a new form – it has become visual. Even if you don't know what the word «meat» looks like, the image of a cow above the store's entrance will instantly inform you of its purpose. The basis of early advertising was a clear link between a product and a service. The blacksmith hung an anvil, the baker a glided pretzel, and the cobbler a wooden shoe. It was just an informational advertisement [1, p. 11].

Advertising was constantly changing, as evidenced by examples such as pop-ups and printing presses. However, both the need for advertising and the methods that ensure its effectiveness remain unchanged. Modern advertising channels include radio, print media (magazines, newspapers), the Internet, direct sales, billboards, newsletters, contests, sponsorship, posters, clothing, events, as well as the use of colors, sounds, visual effects, and even people.

Psychological Impact of Advertisements

Advertisers can target the people who are most likely to buy their products using such classifications. On commercial television, programs try to «package» the audience by showing certain types of shows at certain times. This encourages advertisers to buy time, as it is easier to focus on a specific audience rather than a broad one. For example, television ads often promote certain types of household chemicals, food and beverages, toothpaste, and cars during periods when children are most likely to make up the majority of the audience. As publishers and advertisers become more aware of which people are buying each publication, the target audience of newspapers and magazines becomes clearer. Since advertisers are willing to pay for advertising space in certain newspapers targeted at the affluent middle class, advertisers will be willing to pay for it. Advertising works by arousing consumer interest in a particular product or service. A «sale» or «donation» is likely to occur after a potential consumer has a desire to buy or «donate». Each strategy must be tailored to the target audience, as well as to the type of product or service provided. Some types of advertising are aimed at changing the opinion of the audience. For example, the slogan «The fairy lasts longer» is designed to encourage consumers to prefer one brand over another, convincing them that the product is more successful, fashionable or has a better value for money, even if it is more expensive [4, p. 47].

Other advertising should convince consumers that they need a product that is not necessary in everyday life. Car and perfumes manufacturers, for instance, use the «why?» approach in their advertising. According to research, people remember ads if the product is unique, the ad is unusual, or it has some personal meaning. The visual content and overall design often determine the initial effect. However, it is through the use of language that the identity of a product or service, as well as the brand name, is remembered. The advertising language is usually optimistic, relaxed and informal. Advertisers use vivid, tangible phrases, metaphorical language, and non-standard spelling to make their text (words related to advertising) memorable. Stereotypes are used in marketing because they aim to attract the attention of «typical representatives of certain groups». Women are often seen in homes, and advertisements for bouillon cubes OXO often use the idea of a happy family. With the exception of famous athletes and models, black actors are rarely seen in mainstream advertising campaigns. Advertisers believe that Naomi Campbell, who is attractive to a wide audience, appeared in an advertisement for yogurt and milk «market Müller» [4, p. 48].

In order to trigger particular consumer demands, effective audience segmentation considerably depends on customized visual material and smart language choice. Ultimately, the psychological impact of the advertisement relies on establishing a unique, deeply personal connection that effectively shapes customer behavior.

Forms of Advertising

In the advertising sphere, there are three possible types of communicative interaction, each of which manifests itself in its own way:

*1. **Imitation:** The recipient of the advertisement may unconsciously or consciously repeat the gestures, actions, or behaviors of the information translator.*

*2. **Dialogue**: It is a form of communication where participants recognize each other as equal partners, each with their own set of meanings and values.*

*3. **Management**: In this case, the communicator perceives the recipient as a tool for the realization of his plans, as an object that he seeks to control.*

Having systematized its functions, it is impossible not to pay attention to the economic, informational and social role of advertising. Many other elements are often considered important components of social or informational functions, including cognitive, educational, cultural, ideological, integrative, and communicative functions. Since advertising allows you to perform all its other functions, information and communication are the main functions of advertising. It is used to create and disseminate information on a wide range of topics, including ideas, people, programs, social issues, goods, and services. Consequently, advertising can serve its own ideological, spiritual, and economic goals.

As mentioned above, advertising has undergone various changes, therefore, there are currently diverse forms of advertising.

Direct mail is sent to certain individuals through a mailbox, and themed ads are displayed in thematic contexts targeted at individuals and groups with special interests. Commercial television, radio, cinemas, billboards, newspapers and magazines all contain advertisements aimed at broad consumer groups. Themed ads are shown in contexts targeted at individuals and groups with special interests, and direct mail is sent to specific recipients through the mailbox. All of these commercials are aimed at raising awareness about specific products or services through ads funded by a person or organization for the purpose of educating or influencing a specific audience [4, p. 257-280].

***Outdoor advertising:** Outdoor advertising is a great way to attract the attention of highly mobile groups of the population who spend a significant amount of time on the road, for example, on their way to and from work or as part of their profession.*

***Billboards and banners:** Billboard advertising is still quite popular among business owners. This is especially true in places with a lot of roads.*

***Advertising in retail outlets:** Advertising in retail outlets is very similar. Locals create a postcard and place it where other locals shop, for example, in a supermarket window or in a storefront.*

***Transit advertising:** This is primarily a form of urban advertising that uses bus shelters and taxi tops, as well as posters placed at bus stops, airports, and metro stations.*

***Direct mail** is delivered directly to people's homes and is addressed to individuals who have received it from publicly available sources such as the voter list.*

***Newspapers** are the second most popular means of advertising. With newspaper, advertisers can reach readers of different ages, ethnicities, and income levels.*

***Brochures:** A printed brochure can help many small businesses gain trust and tell your story in more detail.*

***Magazines:** They are designed for a wide range of readers with similar interests. The magazine's ability to reproduce eye-catching color images can enhance the product's appearance [4, p. 257-280].*

All of the above periods and types of advertising show how marketing has flourished over the years, promoting new products and services, revealing well-thought-out strategies and having clear goals. Thus, all types of advertising have their own specific objective, purpose, strategy, and medium.

Conclusion

From simple, early visual indicators, advertising has developed into a complex, multipurpose instrument of mass and focused communication. This historical trend illustrates the strong relationship between marketing strategies, technology literacy, and societal advancement. Regardless of whether advertising is delivered through mass media or personalized channels, each form relies on carefully designed strategies, persuasive language, and audience-oriented communication techniques.

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