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EXPERT ASSESSMENT OF INNOVATIVE ACTIVITIES IN HEALTHCARE

Tamar Shamugia
The Doctoral Student of Georgian Technical University
Tamar Ghambashidze
Doctor of Business Administration
Associate Professor at Georgian Technical University

Abstract

The relevance of the topic is evident in the 2025 innovation performance ranking, where Georgia ranked 47th among 131 countries participating in the Global Innovation Index. This position, on the one hand, reflects systemic contradictions in the development of the national economy, but, on the other hand, does not align with the development goals. The priority for the innovative development of the national economy until 2030 was set by Georgia's Innovation Development Strategy.

The research aims to develop a methodology to ensure the sustainable, innovative development of medical organizations and practical management tools to overcome innovation and socio-economic differentiation.

Scientific novelty of the work. Based on the research conducted: (i) it was established that the combined use of human and social capital and innovative entrepreneurship potential contributes to the balanced economic development of medical organizations; (ii) the architecture of a unified information platform for supporting sustainable innovative development has been developed, based on the principles of timeliness, variability, and simplicity; (iii) a classification and matrix of the goals, directions, and results of the formation of an innovative medical system have been developed.

Keywords: *Expert assessment, innovation, healthcare.*

1. *Literature review*

Level of development of the topic. The problems of innovation, as the basis for the development of economic relations at all levels of the economy, have been the most discussed in the scientific community for decades. The study is based on the fundamental works of foreign and Georgian researchers working in the field of innovation (W. Baumol, V. Govindarayan, K. Christensen, M. Kirton, N. Kondratiev, G. Mensch, G. Chesbro, I. Schumpeter) and sustainable development of systems and economic growth (D. Vollart, T. Jackson, S. Jones, G. B. Kleiner, R. Lucas, E. Helpman).

Amid changing economic conditions, the problems with the institutional foundations of the sustainable development of spatial units are discussed in the works of D. Meadows, R. Rotenberg, and others. The problem of uneven socio-economic development is discussed in P. Minakir's works.

Many studies focus on the formation and use of human and social capital (G. Becker, P. Bourdieu, J. Coleman, B. Milner, R. Vogel, T. Schultz) to ensure economic growth and development. However, identifying the specifics of the formation and development of human capital in the context of the sixth technological paradigm and the transition to a digital economy requires new approaches to its analysis as a source of innovation in economic processes.

2. *Results of expert assessment of innovative activities*

The results of the expert assessment of the organization and planning of information technologies in medical organizations allowed us to identify problem and priority areas for relevant changes in their organization. Among the interviewed experts were 24 leading specialists in healthcare and public health. According to the experts, the following main indicators were identified in the management of medical organizations when organizing information technologies: the need to create an innovative infrastructure (86.4% of experts), structural reorganization (72.1%), new approaches to personnel (63.7%), and innovative forms of organizing the treatment and diagnostic process (64.0%).

According to the majority of experts, planning is the main element of organizing information technologies (92.8%).

64.7% of experts emphasized the need to apply planning principles when organizing information technologies. Among the most promising new technologies for implementation were information (29.4%), organizational and management technologies (33.5%), and modeling (24%). Among the sources

of financing for information security, experts noted targeted government funds (47.2%) and organizations' own savings (27.0%).

In terms of personnel provision, the development of a motivation system (29.8%) and rational organization of the work process (28.7%) were considered important. According to experts, the creation of departments for marketing (36.8%), financial support (33%), legal support (29.0%), and research and development planning (28.0%) was considered crucial for structural reorganization and infrastructure development. Expert assessments of literary sources and dissertation research revealed the main principles of information security planning, which are used in economic spheres of activity. They were formed with the specific features of information security in healthcare in mind.

The principle of scientific validity characterizes the scientific substantiation of management tools and methods used in planning objects and units, carried out in accordance with the laws and trends of scientific, technological, and economic development, and taking into account the objective conditions and specific features of a particular industry. Comprehensive planning implies the systematic coordination of all developed plans in the system, which implies the interconnection and consistency of all stages of planning - from preliminary planning to the development of a general plan and program. Continuous planning is characterized by a constant (cyclic) process of developing, refining, correcting, and expanding plans. Time-based goals must be continually adjusted to remain relevant to healthcare organizations. Social significance is determined by focusing on the public relevance of an idea or plan and should be expressed in the relevance of the problem. Ranking goals by importance requires developing plans for long-, medium-, and short-term.

Table 1. Results of ranking the main planning principles

Areas of focus	Situation	
	Nowadays	In perspective
Creation of a system of state regulation of innovations	3,7±0,08	4,7±0,3
Development of legislation in the field of innovations	3,9±0,5	4,3±0,3
Development of interdepartmental cooperation	4,4±1,2	3,0±0,5
Creation of information databases of innovative technologies, enterprises and innovative projects	3,6±1,7	4,0±1,0
Development of innovative infrastructure	4,6±0,3	4,7±0,3
Creation of a favorable environment and conditions for the development of a competitive environment in the innovation sector	2,9±1,3	4,7±0,3
Adequate innovation management system	4,0±0,5	5

The priorities of goals should take into account their importance, interdependence and logical sequence. The principle of indicator adequacy is expressed in a certain level of compliance with planning criteria. The planned implementation of an innovative product should be ensured by market demand, production capacity and pricing policy. A balanced plan is one of the necessary conditions for the validity of plans and methods, ensuring comprehensive planning, and is based on the interaction among the structural elements of planning. Competent resolution of financing issues is expressed in the economic feasibility of planning, as well as in the economic results of implementing each possible option for the development of an innovative project. The transition from one stage of the plans to another characterizes the continuity of the current and strategic plans. We ranked the proposed principles by importance based on expert assessment (Table 1), thereby substantiating their application in the organization of information security in the healthcare sector.

The proposed principles of information security planning in the healthcare sector help to clarify development goals for the entire organization and each department individually over a specified period; define business goals, means of achieving them, timing and sequence of implementation; and identify the material, labor, and financial resources needed to achieve these goals.

The use of scientific analysis methods derived from the research and the implementation of the developed principles in practical activities will provide healthcare organizations with tools for innovative activity to effectively identify trends in organizational structures, which, in turn, will serve as the basis for planning an innovative model in healthcare.

3. *Status and prospects of innovative activity in healthcare*

The expert assessment revealed that the status and prospects of innovative activity in healthcare include three stages. In the first stage, experts assessed the current state of innovative activity and the challenges in healthcare. At the second stage, experts were asked to assess the prospects for innovative activity, identify the most important areas for development, and mechanisms for implementing them. At the third stage, experts identified risks to innovative activity.

The expert assessment of the status and prospects of innovative activity yielded the following results: According to the interviewed experts, the most developed areas currently include a more or less established innovative infrastructure (4.6 points on a 5-point scale) and interdepartmental interaction (4.4 points). The lowest score is assigned to the existing conditions for developing a competitive environment in the field of innovation (2.9 points). In comparison, the system of state regulation of innovative activity is also rated average (3.7 points).

The most important promising areas for the development of the medical innovation system in healthcare are: the creation of an adequate system for managing innovative activity (5.0 points), the creation of systems of state regulation of innovative activity, the development of innovative activity infrastructure and favorable conditions for the development of a competitive environment in the field of innovations (4.7 points each on a 5-point scale). Experts attach slightly less importance to the development of regulatory legal acts in the field of innovative activity (4.3 points) and the formation of IT, project, and enterprise databases (4.0 points). In the existing innovation management system, "Resource Management" and "Process Management" are most fully represented, but with very low assessment scores (3.3 and 2.6 points, respectively). Experts also gave an extremely low score to the use of strategic management methods in the current management system (1.7 points). For the future development of the innovation management system, the importance of these methods is increasing (4.7 points each); however, experts give priority to the "Strategic Management" block (5 points) (Table 2).

Table 2. The importance of blocks in the existing innovation management system (according to experts' assessment), with scores on a five-point scale

Blocks	Situation	
	Nowadays	In perspective
Resource Management	3,3±1,0	4,7±0,3
Process Management	2,6±1,2	4,7±0,3
Strategy Management (Analysis-Based Long-Term Strategic Planning)	1,7±0,3	5

Among the methods of managing an innovative organization, according to experts, the most important are "organizational development" and "sustainable development" (5 points each), as well as "knowledge management" (4.7 points; Table 3). Experts identified several issues that hinder the development and promotion of innovation.

Table 3. The importance of management methods in organizing innovative activities (according to expert assessment), with scores on a five-point scale

Methods	Situation	
	Nowadays	In perspective
Quality Management	3,7±0,6	4,3±0,3
Reengineering	2,3±1,8	4,3±0,3
Organizational Development Methods	2,6±1,2	5
Structural Reorganization	3,3±0,2	4,0±0,5
Knowledge Management	2,0±1,9	4,7±0,3
Sustainable Development Methodology	1,4±0,4	5

The most important are: the absence of targeted financing of innovative activities and innovative initiatives within the framework of functional systems for the development and promotion of innovations - IDS or Medical Innovation Clusters (MIC) - and, most importantly, the absence of a "consumer" for innovative products (5 points each); the absence of mechanisms and tools for business in the field of innovative activities; the lack of interest in innovative products among health authorities and managers of medical organizations at all levels (4.7 points each); and the limited use of PPP opportunities (4.5 points).

Table 4. The importance of innovative issues in healthcare (according to expert assessments), with points on a five-point scale

Problems	Situation	
	Nowadays	In perspective
Limited research on relevant scientific topics	3,9±0,7	3,7±0,3
The existing scientific, educational and practical healthcare system	4,7±0,7	4,7±0,7
Problems of implementing medical innovations and ensuring their accessibility for both specialists and patients	4,6±0,7	4,6±0,3
Lack of mechanisms for targeted financing of innovations and attracting investments	5	4,7±0,3
Limited use of public-private partnership opportunities	4,5±0,7	4,7±0,3
Lack of mechanisms and tools for business in the field of innovations	4,7±0,8	4,7±0,3
Lack of infrastructure and innovative environment or cluster organization for implementing the stages of the innovation cycle	4,4±0,7	5
Lack of interest at all levels of healthcare management	4,3±0,8	4,7±0,3
Lack of interest among managers of medical organizations	3,9±0,3	5,0±0,0
Insufficient awareness of consumers of medical products and services about innovations in healthcare	3,9±0,8	4,7±0,3
Lack of a "consumer" for an innovative product	4,7±0,8	5

Some problems are primarily related to the widespread introduction of medical innovations and, consequently, to ensuring their accessibility for both specialists and patients (4.6 points each), as well as circumstances that prevent the solution of these problems within the framework of the existing, long-established and familiar system of scientific, educational activities and practical healthcare (4.7 points). The state of development of healthcare and medical science is also characterized by a low level of infrastructure development, which would transfer scientific research to practical healthcare (4.6 points), Table 4.

The most important areas for improving the efficiency of innovations in healthcare are the creation of specialized institutions (infrastructure facilities) and innovation platforms (5.0 points), increasing the volume of innovation financing and developing mechanisms for attracting investments (4.7 points), and implementing training programs for innovations (4.5 points), Table 5.

Table 5. Importance of areas for improving the efficiency of innovations in healthcare (according to expert assessment), with scores on a five-point scale

Directions	Situation	
	Nowadays	In perspective
Increasing financing of innovative activities through the creation and implementation of mechanisms for attracting investments	2,9±0,9	4,7±0,3
Implementation and implementation of innovative training programs	3,0±1,1	4,5±0,3
Creation of specialized institutions (infrastructural facilities), innovative platforms and other elements of the innovative environment	3,0±0,1	5

Of the existing innovation platforms, according to experts, the most important are clinics that introduce and implement IT (4.6 points on a 5-point scale), followed by research centers in research institutes (4.3 points) and the least represented in IMS (3.3 points). The most important and promising innovation platforms are industry-specific innovation cluster structures, technology parks and business incubators (4.7 points each), as well as innovation clinics (4.6 points). Experts named medical manufacturing companies as the most important "users" of innovative products and technologies operating in this sector (4.3 points).

Pharmaceutical companies and medical businesses are currently less important (4.1 points), while medical organizations created within the framework of public-private partnerships (3.7 points) are given an average importance. The role of medical organizations of various legal forms (2.4-2.0 points) and public associations of patients with various pathologies (1.7 points) in this sector is insignificant; however, according to literary sources and logical data, this contingent may be the target consumer who is most interested in reproducing the necessary parameters of innovative products.

Table 6. Importance of potential users of innovative medical products and technologies (according to expert assessment), with points on a 5-point scale.

Clients	Situation	
	Nowadays	In perspective
Public healthcare organizations	2,0±1,7	4,0±0,5
Private (non-governmental) healthcare organizations	1,4±1,4	3,7±0,3
Public-private partnership medical organizations	3,7±0,7	5
Pharmaceutical companies and healthcare businesses	4,1±0,7	5
Medical manufacturing companies	4,3±0,9	5
Public associations of patients with certain diseases	1,7±0,2	4,0±0,5

Experts identified the same potential users of innovative medical products and technologies as the most promising, but with greater weight: medical organizations within the framework of public-private partnerships, pharmaceutical companies and medical businesses, as well as medical manufacturing companies (5 points each), Table 7.

According to experts, currently in the areas of development of the innovative medical system, attention is paid only to increasing the efficiency of scientific and educational potential and ensuring interaction between the elements of the innovative medical system through an effective coordination and management system, and even then not to the necessary extent (3.9 and 3.7 points, respectively).

Low scores were given to the current state of infrastructure development (3.1 points) and to the availability of support for innovative businesses and the formation of demand for innovations (both 3.0 points).

A negligible score was assigned to the level of integration into the global information system (2.3 points), the presence of a system for implementing innovative projects (IP), which ensures entry into the IT market, and the existence of an innovative culture in society (1.9 points each).

The priority areas for the development of the infrastructure of an innovative medical system are the development of innovative infrastructure; ensuring interaction between elements of the environment through an effective coordination and management system (5 points each); and integration into the global innovation system through the implementation of technological and research projects that provide breakthrough positions in scientific and technological competition (4.9 points), Table 7.

Table 7. The importance of areas for developing the infrastructure of an innovative environment in regional healthcare (according to expert assessment), with scores on a 5-point scale.

Directions	Situation	
	Nowadays	In perspective
Support for innovative business and generation of demand for innovations	3,0±0,8	4,0+0,5
Increasing the effectiveness of scientific and educational potential	3,9±0,4	4,0+0,5
Development of innovative infrastructure	3,1±1,0	5
Integration into the global innovation system	2,3±1,9	5
Implementation of a system of technological and research projects that ensures breakthrough positions in scientific and technological competition	1,9±2,4	4,9±0,1
Ensuring interaction between environmental elements through an effective coordination and management system	3,7±0,5	5
Development of an innovative culture in society and raising the status of innovators	1,9±1,1	3,7±0,3

The most effective organizational form for IT implementation is currently a public-private partnership (3.9 points). The importance of this organizational form will only increase in the future (5.0 points). The most effective form of public-private partnership as the basis for investments in healthcare is the transfer of facility ownership by the private partner upon completion of construction (5 points), Table 8.

The most important areas for creating a favorable economic climate for innovative activities in healthcare are systematic, comprehensive state support and the development of an adequate system to organize and manage such activities. Experts rated these areas equally for both the current situation (3.6 and 3.1 points) and future development (4.7 points each), only with different numerical values (Table 9).

Table 8. The importance of public-private partnership forms as a basis for innovative activities in the healthcare sector (according to expert assessment), with scores on a five-point scale

Forms	Situation	
	Nowadays	In perspective
Concession (construction, right of use during the term of the contract, with subsequent transfer to the state)	2,9±1,2	3,7±0,3
Ownership remains with the private partner during the term of the contract	3,3±1,9	3,7± 1,3
Life cycle contract (the facility is transferred to the state after construction)	2,4±1,4	4,0±1,0
Ownership of the facility by the private partner after completion of construction	4,4±2,0	5
Ownership remains with the public partner	2,0±0,9	1,0±0,3

Table 9. The importance of areas for creating a favorable economic climate for innovative activities in healthcare (according to expert assessment), with scores on a five-point scale.

Directions	Situation	
	Nowadays	In perspective
Active use of marketing tools	2,6±1,2	3,0±1,0
Development of an adequate system for organizing and managing innovative activities	3,1±1,0	4,7±0,3
Sustainable development of healthcare	2,4±1,4	4,0±0,1
Systemic and comprehensive state support	3,6±0,8	4,7±0,3

The assessment of sources of financing for innovative activities reflected the government's absolute participation through funds from innovative activity support funds (4.3 points) and targeted funding

(3.9 points), as well as competitive and grant activities (4.1 points), which can be classified as state sources.

Other sources of financing, including internal savings from extrabudgetary sources, charitable donations, etc., are presented with very low estimates (from 2.0 to 1.6 points).

In addition to the above-mentioned grants and competitions (5.0 points), experts identified state funding from innovative activity support funds, internal savings of medical organizations or associations, "technological development funds", and targeted state funding (4.6 points) as the most important promising sources of investment in innovative activities. Less weight is given to the financing of large commercial companies producing pharmaceutical products, structures, equipment, and consumables (4.5 points) in the evaluation scale, even though, according to the literature (Table 10), this is one of the leading financial flows in the global medical innovation market.

Experts identified the Department of Advanced Scientific Planning for Fundamental and Applied Research as the most important infrastructural unit (a division of various organizations) in the current innovation system, albeit with a relatively low score (3.7 points).

Table 10. Importance of investment sources in innovative activities (according to experts' assessment), with scores on a five-point scale

Forms	Situation	
	Nowadays	In perspective
State target funds	3,9±0,3	4,6±0,3
Funds received from grants and competitions	4,1±0,5	5
Charitable funds	2,0±1,2	3,0±0,8
State funds received from innovation support funds	4,3±0,6	4,7±0,3
Funds of large commercial companies producing pharmaceutical products, structures, equipment and consumables	3,0±0,2	4,5±0,2
Funds of public organizations and foundations interested in the development and popularization of innovative products (diabetes and hemophilia associations, etc.)	1,6±0,8	3,0±1,3
Funds outside the budget of medical organizations for the provision of paid services to the public	1,6±1,1	20±1,1
Internal savings funds of medical organizations or associations in an innovative environment/ "Technological development funds"	1,6±1,3	4,7±0,3

Even lower scores were assigned to the following blocks: conducting clinical trials (3.4 points), research and development, engineering technologies (3.3 points), conducting preclinical studies (3.1 points), information support (3.0 points), developing prototypes of innovative products (2.9 points), developing medical technologies and certifying a product or technology (2.7 points), and marketing research and replication and ensuring the security of intellectual property rights (2.4 points each).

Based on these scores, we can judge the weak development of individual elements of the intellectual property system and the absence of a system to coordinate their activities, creating the overall impression of an underdeveloped IMS infrastructure.

Table 11. Importance of training bases for innovative activities (according to experts' assessment), with scores on a five-point scale

Bases	Situation	
	Nowadays	In perspective
Specialized departments (specialized courses in programs) at universities	2,6±1,8	3,3±0,3
Research and educational centers (research and educational complexes) at universities and research institutes with bases	3,3±1,0	4,3±0,3
Educational centers in industrial clusters	2,7±1,4	5
Centers for professional retraining and certification	1,9±1,5	2,3±0,3

According to experts, the high importance of the formation and further development of IMS or MIC for the prospective scientific planning block of fundamental and applied research should be maintained (4.7 points). The departments of research and development and engineering technologies, the development of innovative product prototypes, clinical and preclinical studies, and the protection of intellectual property rights were assessed by experts at 4.3 points on a five-point scale. According to experts, the most important perspective training bases for innovative activities are educational centers of the microindustrial complex (5 points) and regional centers, or regional centers located at universities or research institutes (4.3 points), Table 11.

When assessing the importance of indicators of the innovative potential of medical organizations, the opinions of experts were distributed as follows: material-technical and scientific-educational bases, human resources and financial and economic activities (5 points each), organizational structure and management system of the organization (4.6 points each), Table 12.

Table 12. The importance of indicators for assessing the innovative potential of medical organizations (according to expert assessment data), with scores on a five-point scale

Indicators	Situation	
	Nowadays	In perspective
Organizational structure	3,6±1,5	4,6±0,3
Material and technical resources	4,3±1,2	5
Financial and economic activities	4,0±1,4	5
Human resources	4,6±1,2	5
Scientific and educational resources	4,6±1,0	5
Organizational management system	3,6±1,3	4,6±0,3

The experts' opinion on the importance of indicators of the effectiveness of the introduction of innovations in healthcare is as follows:

• Ensuring the quality of medical services and improving medical and demographic indicators (5 points each),

• Development of high technologies in medicine and satisfaction of medical service (care) users (4.7 points),

• Increasing the motivation of medical personnel for professional growth and qualification improvement (4.0 points),

• Attracting additional funds for the development of medical organizations and raising their status (2.9 points), Table 13.

XV compliance coefficient was 0.76.

Expert assessment of intellectual property risks yielded the following results.

Experts assessed the importance of the factors determining intellectual property risks in healthcare as follows (scored on a five-point scale):

- Probability of lack of state support for intellectual property - 4.8 ± 0.2 points;

- Lack of stable contacts between the user and the creator of the innovative product, user unreliability, vague formulation of technical specifications, etc. - 4.4 ± 1.1;

- Long project implementation time - 4.3 ± 0.5;

- Probability of incomplete IT or product registration cycle - 4.3 ± 1.1;

- High level of initial investment - 4.1 ± 0.7;

- Absence of a legal and regulatory framework regulating the activities declared in the innovation project - 4.1 ± 1.0;

- Lack of infrastructure elements for the implementation of a full innovation cycle for a specific individual entrepreneur - 3.9 ± 0.7;

- Probability of absence of private investments - 3.8 ± 0.8;

- Absence of information support for an individual entrepreneur - 3.6 ± 0.3;

- Other - 1.3 points.

Table 13. Importance of indicators of effectiveness of innovation implementation in healthcare (according to expert assessment), with scores on a five-point scale

Indicators	Situation	
	Nowadays	In perspective
Attraction of additional resources for the development of medical organizations and raising their status	3,0±1,5	2,9±0,5
Satisfaction of medical service (care) users	4,3±0,6	4,7±0,7
Increasing the motivation of medical personnel for professional growth and qualification improvement	4,0±0,5	4,0±0,3
Ensuring the quality of medical service (care)	4,9±0,1	5
Development of high (science and resource-intensive) technologies in medicine	4,7±0,2	4,7±0,1
Improvement of public health indicators and demographic data	5	5

Thus, according to the expert assessment, the main risk for an individual entrepreneur is the likelihood of a lack of state support. The leading risks are: the absence of stable contact between the customer and the creator of the innovative product; the customer's non-binding nature; vague formulation of technical specifications; long project implementation time; and the likelihood of incomplete IT or product registration cycles. An expert assessment of the current state of information technologies in healthcare showed that the most developed areas of existing information systems are, more or less, established innovative infrastructure and interagency cooperation. The lowest rating is given to the current conditions for developing a competitive environment in the innovative medical system, and the state regulation system for innovative activities is also rated average. The existing system of innovative activity management includes the blocks of "resource management" and "process management", although their

performance indicators are very low. Experts also gave an extremely poor assessment of the use of strategic management methods in the current management system. According to experts, pharmaceutical companies are ready to introduce medical innovations at the current stage of healthcare development. Laboratory activities and diagnostics received a lower, but significant score. Clinical areas (surgery, rehabilitation, and therapy) were assessed as poorly prepared. Of particular interest is the expert assessment of the readiness to introduce innovations in healthcare management, which was quite average. This fact reflects a certain pessimism among the heads participating in the survey about the existing system, current methodologies, and overall effectiveness of management.

According to experts, the importance of organizational and managerial technologies in the development of individual entrepreneurship is low. Innovative treatment and diagnostic technologies are also assessed at a similar level. According to experts, these technologies should be given greater priority to advance information technology. Their assessment indicators increased in the process of identifying promising technologies. The analysis of expert opinions revealed problems in information technology (innovative activities) that hinder the development and promotion of innovations in healthcare and medical science. The most important problems are: lack of targeted funding; absence of functional systems to ensure the development and promotion of innovations; absence of a "user" for innovative products; absence of mechanisms and tools for business to work in the field of innovative information technologies; lack of interest in innovative products among executives at all levels of healthcare and leaders of medical organizations; limited use of opportunities for private-public partnerships.

There are challenges mainly related to the widespread distribution of medical devices and, consequently, to ensuring their accessibility for both specialists and patients, as well as circumstances that prevent the resolution of these issues within the existing, long-established and familiar system of scientific, educational and practical healthcare. The state of development of healthcare and medical science is also characterized by underdeveloped infrastructure that would facilitate the translation of scientific research into practical healthcare (4.6 points).

A low score is assigned to the current state of support availability for innovative businesses and the generation of demand for medical devices. The opinions of experts regarding the importance of innovative efficiency indicators in healthcare are as follows: ensuring the quality of medical services and improving medical and demographic indicators, developing high technologies in medicine and customer satisfaction with medical services, increasing the motivation of medical personnel for professional growth and qualification improvement, attracting additional funds for the development of medical organizations and raising their status.

The research conducted allowed us to create a matrix of goals, directions, and results for the development of an innovative medical system, which is presented in the following subsection.

4. ***Matrix of goals, directions and results of the formation of an innovative medical environment***

I. State regulation of innovative activities

- *Development of targeted programs for the development and implementation of innovative activities in healthcare*
- *Development of mechanisms for interaction between government and business in the implementation of innovative processes, including mechanisms for the formation of strategic government-business partnerships*
- *Development of educational programs in the field of innovation, promotion and support of innovative personnel*
- *Development of mechanisms for interagency interaction.*

Goal: *Effective state regulation and support of innovative activities.*

Results:

- *Reducing the risks of innovative activities*
- *Introducing a social component in the field of innovation*
- *Increasing the investment attractiveness of medical and scientific organizations*

II. Economic climate and financing

- *Attracting private investments in the industry with state guarantees through the private partnership mechanism.*
- *Formation of private accumulation funds/"technological development funds" for medical organizations or associations in an innovative environment.*

Goal: *Creating effective financial management levers in the innovative sector.*

Result: *Creating conditions for the inclusion of market mechanisms in IMS*

Goal 3: Creation of effective mechanisms and tools to develop a medical information system.

Results:

- *Reduction of the term of validity of intellectual property (ensuring faster results); Formation of a proactive position regarding innovations;*
- *Creation of specialized institutions and infrastructure facilities for the implementation of innovative activities: technology parks, clusters, prototyping centers (platforms for the development of innovative product models and IT implementation), REC/QCs.*
- *Creation of financial and legal conditions to ensure interagency interaction.*
- *Creation of models of promising innovative clinics.*
- *Creation of elements and services supporting the infrastructure of the information system: service companies, marketing companies, legal support for innovative activities, financial infrastructure, etc.*

Goal 4: Ensuring a full cycle of innovative activities, from the development of innovative activities to the implementation of IT in healthcare practice.

Results:

- *Proven mechanisms for transferring IT to the real sector of the economy*
- *Established communication between the "user" and "user" of innovative products and technologies*
- *Self-regulation mechanism for generating requirements of users/consumers of innovative products.*
- *Creation of specialized institutions and infrastructure facilities for the implementation of innovative activities: technology parks, clusters, prototyping centers (platforms for developing innovative product models and IT implementation), REC/QCs.*
- *Creation of financial and legal conditions to ensure interagency interaction.*
- *Creation of models of promising innovative clinics.*
- *Creation of supporting elements and services of the information system infrastructure: service companies, marketing companies, legal support for innovative activities, financial infrastructure, etc.*
- *Increasing the investment attractiveness of healthcare*

IV. Management of innovative activities in healthcare

Development of scientifically substantiated models of innovation management.

Goal 1: Ensuring interaction between IMS elements through effective coordination of innovations and the management system.

Results:

- *Increasing satisfaction of the needs of innovation participants*
- *Development of new needs of innovation participants and users*
- *Improving the capabilities of medical and scientific organizations*
- *Development of intellectual capital in the field of innovation. Creation of sustainable functional models*
- *Integration of total quality management, knowledge management, sustainable development, and organizational development methodologies into the management system*
- *Ensuring the continuity of integrated service delivery and innovation process chains.*

Goal 2: Integration of resource, process, and strategic management methods into the innovation activities management system.

Results:

- *Development of a permanent system that improves resource efficiency*
- *and realizes the high potential for optimizing business processes and improving healthcare delivery methods.*
- *Creation of basic conditions for the involvement of medical organizations in innovative activities within the framework of IMS.*
- *Improvement of the social status of medical organizations*
- *Improvement of investment attractiveness of healthcare*
- *Development of a proactive approach to innovative activities among leaders of all levels of healthcare*

Goal 3: Increasing the readiness of medical organizations to reproduce and implement innovative technologies.

Results:

• *Generating demand for innovative products in the medical community*
• *Creation of centers for prototypes of treatment and diagnostic technologies and innovative clinical models as elements of IMS*
• *Ensuring the quality and accessibility of medical services*
• *Using new and innovative treatment and diagnostic technologies (satisfaction of medical users)*
• *Improving medical and demographic indicators*
• *Development of high-tech medical services*
• *Improving the investment attractiveness of medical organizations*

V. Information support of healthcare

• *Creation of IT information databases*
• *Creation of information databases of innovative enterprises*
• *Creation of information databases of individual entrepreneurs*
• *Creation of a registry of experts in leading areas of innovation*
• *Development of telemedicine technologies*

Goal: Development of the concept of a systematic approach to information
Support for innovations in healthcare
Results: Information database Creation of a full range of bases

VI. Scientific and educational activities in the field of healthcare

• *Creation of regional and national energy centers (REC) and national energy centers (NEC) within the framework of cluster structures.*
• *Further development of research areas of research institutes.*
• *Active development of innovative activities based on cooperation of various innovative entities, primarily through the establishment of links with practical healthcare.*
• *Implementation of interagency interaction.*

Goal 1: Formation of a new type of relationship and interaction between science, education and practical healthcare.
Results: A self-sustaining system for generating new knowledge.
• *Active use of basic platforms for innovative training in universities and research institutes.*
• *Development and implementation of innovative training programs.*

Goal 2: Improving the quality and level of training of science and innovation specialists.
Results:
• *Creation of an environment for continuous education of information technology specialists: innovators and innovation managers.*
• *Provision of professional personnel for the commercialization of scientific research and development.*

Conclusion

Thus, a comprehensive expert assessment of the state and prospects of innovative healthcare, conducted using statistical and economic analysis methods and based on the opinions of experts working in the fields of management, healthcare organization, medicine and business, showed the existence of the main conditions and prerequisites for the formation of innovative medical systems in this area, and also made it possible to identify several problems limiting the development, popularization and implementation of innovative medical systems.

The analysis revealed intellectual property risks, the main of which are: the absence of stable contacts between the consumer and the creator of the innovative product, the absence of consumer obligations, vague formulation of technical specifications, etc.; long project implementation times and the possibility of incomplete registration of an innovative technology or product. But the main risk always remains the possibility of a lack of state support. An integrated information system developed using scientific analysis and modeling methods, with a developed infrastructure, management and coordination system, appropriate regulatory framework and support, will facilitate the implementation of a closed-loop process from scientific ideas to the implementation of IT and innovative products in healthcare practice, as well as the implementation of effective information management in healthcare and medical science. This model can become a step towards the formation of a more organized and sophisticated system - an integrated information system - at the regional level.

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Jurisprudence

ACADEMIC FREEDOM AND INTERNATIONAL LAW

Medvedieva Maryna
Doctor of Law, Professor at the International Law Chair
Educational and Scientific Institute of International Relations
Taras Shevchenko National University of Kyiv

АКАДЕМІЧНА СВОБОДА ТА МІЖНАРОДНЕ ПРАВО

Медведєва Марина
доктор юридичних наук, професор, професор кафедри міжнародного права
Навчально-науковий інститут міжнародних відносин
Київського національного університету імені Тараса Шевченка

1. Вступ.

Академічна свобода є фундаментальною цінністю будь-якого демократичного суспільства. Вона включає свободу осіб вільно висловлювати свою думку про установу чи систему, в якій вони працюють, виконувати свої функції без дискримінації чи страху репресій з боку держави або будь-якого іншого суб'єкта, брати участь у професійних чи представницьких академічних органах та користуватися всіма міжнародно визнаними правами людини, що застосовуються до інших осіб у тій самій юрисдикції [1]. Академічна свобода охоплює індивідуальні та інституційні права і тягне за собою різні зобов'язання для державних органів, оскільки вона поширюється не лише на членів академічної спільноти, а й на освітні установи, і може бути належним чином реалізована за умови створення державою відповідних правових, організаційних і фінансових гарантій.

Академічна свобода тісно пов'язана з низкою прав людини, зокрема правом на свободу вираження поглядів та свободу думки, правом брати участь у культурному житті, включаючи право користуватися результатами наукового прогресу, правом на захист моральних і матеріальних інтересів, що є результатом будь-якого наукового, літературного чи художнього твору, правом на свободу, необхідну для наукових досліджень і творчої діяльності. Академічна свобода захищена статтею 54 Конституції України та Законом України «Про вищу освіту» (статті 1, 2, 57).

2. Захист академічної свободи на рівні універсального міжнародного права.

Відповідно до статті 15 Міжнародного пакту про економічні, соціальні та культурні права, держави-учасниці зобов'язуються поважати свободу, необхідну для наукових досліджень та творчої діяльності. 30 квітня 2020 року Комітет ООН з економічних, соціальних та культурних прав опублікував Загальний коментар № 25 щодо науки та економічних, соціальних та культурних прав, у якому підкреслив, що свобода досліджень включає такі виміри: захист дослідників від неналежного впливу на їхні незалежні судження; можливість для дослідників створювати автономні дослідницькі установи, визначати цілі та завдання дослідження й методи, які мають бути застосовані; свобода дослідників вільно та відкрито ставити під сумнів етичну цінність певних проєктів та право відмовитися від участі в них, якщо це обумовлено їхніми уявленнями про етичність чи справедливість; свобода дослідників співпрацювати з іншими дослідниками, як на національному, так і на міжнародному рівні; обмін науковими даними та аналізом з політиками та громадськістю, де це можливо [2]. В іншому Загальному коментарі № 13 до статті 13 щодо права на освіту Комітет зазначив, що, незважаючи на відсутність згадки про академічну свободу в зазначеній статті, він вважає за необхідне висловити низку зауважень щодо цього питання, а саме: користування академічною свободою передбачає обов'язок поважати академічну свободу інших, забезпечувати справедливе обговорення протилежних поглядів і ставитися до всіх без дискримінації за будь-якою із заборонених ознак [3].

Комітет ООН з прав людини розглядав академічну свободу крізь призму статті 19 Міжнародного пакту про громадянські та політичні права, яка закріплює право мати власну думку та свободу вираження поглядів, у таких справах, як Faurisson v. France [4] та Adimayo M. Aduayom and Others v. Togo [5]. Згідно з обставинами першої справи, Роберт Форіссон, французький письменник і професор літератури в Університеті Сорбонна, засумнівався в існуванні газових

камер для знищення євреїв в Освенцимі та інших нацистських концтаборах під час Другої світової війни. 13 липня 1990 року законодавча влада Франції ухвалила «Закон Гейссо», який вносить зміни до Закону про свободу преси 1881 року. Фориссон оскаржив Закон 1990 року, згідно з яким заборонялося оспорювання існування категорії злочинів проти гуманності, стверджуючи, що це обмежує його право на свободу вираження поглядів. Комітет вирішив, що обмеження свободи вираження поглядів заявника було виправданим з огляду на необхідність боротьби з антисемітизмом і захисту прав інших осіб та постановив, що будь-яке таке обмеження має в сукупності відповідати таким умовам: воно повинно бути передбачено законом, переслідувати одну з цілей, викладених у пункті 3 (a) і (b) статті 19 та бути необхідним для досягнення законної мети.

У справі Adimayo M. Aduayom and Others v. Togo двоє авторів повідомлень були викладачами університетів, яких було заарештовано та звинувачено у поширенні документів, які критикували політику Того. Комітет постановив, що дії держави порушили статтю 19 Пакту про свободу вираження поглядів та інформації. Стосовно цієї статті він зазначив, що свобода інформації та вираження поглядів є наріжними каменями будь-якого вільного та демократичного суспільства. Суть таких суспільств полягає в тому, що їхнім громадянам має бути дозволено відкрито й публічно оцінювати свої уряди, не боячись втручання чи покарання, у межах, встановлених статтею 19. Комітет дійшов висновку, що, незважаючи на те, що викладачі університету в цьому випадку були частиною державної служби (університет був підконтрольний державі), вони мали право бути політично активними та критикувати уряд. Комітет також визнав порушення статті 25(c), яка захищає доступ до державної служби задля захисту академічної свободи авторів.

Ще в 1988 році Всесвітня університетська служба схвалила Лімську декларацію про академічну свободу та автономію закладів вищої освіти, в якій академічна свобода визначається як свобода членів академічної спільноти в отриманні, розвитку та передачі знань, що здійснюються на індивідуальній чи колективній основі, шляхом досліджень, навчання, дискусій, документування, виробництва, створення, викладання або письма.

У 2020 році Спеціальний доповідач ООН з питань просування та захисту права на свободу думки та вираження поглядів опублікував доповідь про захист академічної свободи відповідно до міжнародного права [6]. Для продовження цієї ініціативи було створено Робочу групу з питань академічної свободи, яка ухвалила Принципи реалізації права на академічну свободу та представила їх для публічного обговорення протягом 2023-2024 років. В документі викладено такі принципи: академічна свобода – це право на розвиток знань та ідей; академічна свобода захищена міжнародним правом прав людини; академічна свобода вимагає автономії навчальних закладів; академічна свобода включає внутрішньоінституційне та позаінституційне вираження думок; академічна свобода вимагає доступу до інформації; академічна свобода вимагає свободи пересування та об'єднань; академічна свобода є важливою для всіх рівнів освіти; студенти мають право на академічну свободу; повага, захист та просування академічної свободи є спільною відповідальністю [6].

На 52-й сесії Ради ООН з прав людини, яка відбулася у квітні 2023 року, Франція від імені 72 країн представила спільну заяву щодо академічної свободи [7]. Заява підтверджує життєво важливу роль академічної свободи та закликає всі держави захищати й розвивати її як наріжний камінь демократії та прав людини. У спільній заяві визнається критична роль, яку відіграють університети та академічні установи у сприянні критичному мисленню, креативності та інноваціям, а також підкреслюється важливість захисту академічної свободи як оплоту проти авторитаризму та засобу для сприяння відкритим і демократичним суспільствам.

3. Захист академічної свободи на рівні регіонального міжнародного права.

На європейському рівні стаття 13 Хартії основоположних прав Європейського Союзу прямо передбачає, що академічна свобода має бути захищена. В 2012 році Комітет Міністрів Ради Європи ухвалив Рекомендацію державам-членам щодо відповідальності державних органів влади за академічну свободу та інституційну автономію. Ця рекомендація стосується ролі та відповідальності державних органів влади у просуванні інституційної автономії та академічної свободи як важливих рис національних систем освіти, а також європейської вищої освіти та цінностей, що лежать в основі Європейського простору вищої освіти. Разом з тим, як наголошується в документі, академічна свобода та інституційна автономія не є абсолютними та спираються на баланс, який може бути забезпечений лише шляхом громадських обговорень та консультацій.

Стаття 10 Конвенції про захист прав людини та основоположних свобод встановлює, що кожен має право на свободу вираження поглядів, яка включає свободу дотримуватися своїх поглядів та отримувати й поширювати інформацію без втручання державної влади та незалежно від кордонів. Це право може бути піддане лише таким обмеженням, які передбачені законом, є необхідними в демократичному суспільстві та є пропорційними. Європейський суд з прав людини (далі – ЄСПЛ) підкреслив важливість академічної свободи відповідно до статті 10 у низці своїх справ, наприклад, Sorguç v. Turkey, Aksu v. Turkey, Mustafa Erdoğan and Others v. Turkey.

Згідно з обставинами справи Sorguç v. Turkey [8], професор університету розкритикував систему призначення у своєму закладі вищої освіти на конференції, а згодом доцент подав на нього позов до суду за образу його репутації. Національний суд виніс рішення проти професора, погодившись, що його зауваження становлять напад на репутацію колеги. ЄСПЛ постановив, що держава порушила статтю 10 Європейської конвенції, оскільки національний суд надав більшого значення репутації неназваної особи, ніж свободі вираження поглядів, якою зазвичай має користуватися науковець під час публічних дебатів. Суд підкреслив важливість академічної свободи, яка включає свободу науковців вільно висловлювати свою думку про установу чи систему, в якій вони працюють, і свободу поширювати знання та правду без обмежень.

У справі Aksu v. Turkey [9] ЄСПЛ заявив, що його прецедентне право вимагає від нього піддавати ретельному розгляду будь-які обмеження свободи науковців проводити дослідження та публікувати свої висновки. У 2000 році Міністерство культури Туреччини видало книгу під назвою «Цигани Туреччини», написану доцентом університету. Заявник (пан Аксу) стверджував, що книга містить зауваження та вислови, які принижують циган, і згодом подав позов про відшкодування збитків проти Міністерства та автора книги. Суд першої інстанції відхилив позов після того, як встановив, що книга є результатом академічного дослідження, ґрунтується на наукових даних і досліджує соціальні структури циган у Туреччині, а також що стверджувані висловлювання не ображають заявника. Це рішення було залишено в силі апеляційним судом. Тим часом заявник також подав цивільний позов проти неурядової асоціації, яка за фінансової допомоги Міністерства культури видала два словники під назвами «Турецький словник для учнів» і «Турецький словник», які, як стверджував заявник, містили певні образливі та дискримінаційні висловлювання щодо ромів. Національні суди також відхилили цю вимогу, встановивши, що визначення та вирази в словнику ґрунтуються на історичній та соціологічній реальності, і що не було наміру принизити будь-яку етнічну групу. У своєму рішенні 2010 року ЄСПЛ постановив, що порушення державою прав заявника згідно зі статтею 14 Конвенції (недискримінація) у поєднанні зі статтею 8 (приватне та сімейне життя) не було. Суд вирішив, що національні органи влади не вийшли за межі свободи розсуду та не знехтували своїм позитивним зобов'язанням забезпечити заявнику ефективну повагу до його прав. Таким чином, в цьому рішенні Суд підтримав академічну свободу науковців.

У справі Mustafa Erdoğan and Others v. Turkey [10] ЄСПЛ зазначив, що академічна свобода в дослідницькій діяльності має гарантувати свободу вираження поглядів, свободу поширення інформації та свободу проведення досліджень і поширення знань та правди без обмежень. Він зробив важливий висновок про те, що академічна свобода надає науковцям право вільно висловлювати свої погляди та думки, навіть якщо вони є суперечливими чи непопулярними, у межах їхніх досліджень, професійних знань та компетенції.

Африканська комісія з прав людини та народів у рішенні в справі Kenneth Good v. Republic of Botswana [11] захистила академічну свободу через свободу вираження поглядів згідно з Африканською хартією прав людини та народів. У лютому 2005 року Кеннет Гуд, австралійський викладач Університету Ботсвани, став співавтором газетної статті, яка критикувала політичну спадкоємність у Ботсвані. Пізніше того ж місяця президент Ботсвани оголосив Гуда «небажаним жителем або відвідувачем Ботсвани» відповідно до розділу 7(f) Закону Ботсвани про імміграцію. Гуду не було пояснено жодних причин цього рішення, а також він не мав доступу до механізму, за допомогою якого міг би оскаржити його в адміністративному порядку. Гуд звернувся до Високого суду, який постановив, що виконання президентом своїх повноважень відповідно до розділу 7(f) не підлягає перегляду. У день, коли Верховний суд виніс рішення, Гуд був депортований з Ботсвани. Потім Гуд подав апеляцію до апеляційного суду, який також відхилив його аргумент, постановивши, що президент, роблячи такі заяви, має право діяти в інтересах країни без судового нагляду. Пізніше Гуд звернувся до Африканської комісії, стверджуючи, що розділ 7(f) і положення, які дозволяли президенту відмовлятися вказувати причини депортації, не відповідають Африканській хартії. Гуд стверджував, що рішення президента порушило його права згідно зі статтею 9, яка

передбачає, що кожна особа має право отримувати інформацію та право висловлювати й поширювати свою думку в межах закону. Посилаючись на Декларацію принципів свободи вираження поглядів в Африці, Комісія підтвердила, що обмеження щодо реалізації прав є допустимими лише тоді, коли вони передбачені законом, слугують законним інтересам і є необхідними в демократичному суспільстві. Комісія постановила, що дії президента щодо депортації Гуда були непотрібними, непропорційними та несумісними з практикою демократичних суспільств, міжнародними нормами прав людини та Африканською хартією. Комісія рекомендувала Ботсвані надати Гуду адекватну компенсацію та вжити заходів для приведення Закону про імміграцію у відповідність до міжнародних стандартів прав людини, зокрема до Африканської хартії.

4. Висновки.

Таким чином, академічна свобода, як і інституційна автономія, є невід'ємною складовою демократичного суспільства, розвитку науки та забезпечення права на освіту. Міжнародно-правові акти універсального й регіонального рівнів розглядають її як комплексне право, що охоплює свободу наукових досліджень, викладання, поширення результатів наукової діяльності, участь в академічному самоврядуванні та відкрите висловлення професійних поглядів. Водночас академічна свобода не є абсолютною, однак її обмеження допускаються лише за умови, що вони встановлені законом, переслідують легітимну мету, є необхідними та пропорційними в демократичному суспільстві.

Практика міжнародних контрольних органів, зокрема Комітету ООН з прав людини, Комітету ООН з економічних, соціальних і культурних прав, Європейського суду з прав людини та Африканської комісії з прав людини та народів, демонструє послідовний підхід до захисту академічної свободи як важливого елемента свободи вираження поглядів і наукової діяльності. Їхні рішення підтверджують, що науковці мають право критикувати державну політику, діяльність своїх установ, брати участь у суспільних дискусіях та поширювати результати досліджень без необґрунтованого втручання з боку держави. Водночас судова практика свідчить про необхідність досягнення справедливого балансу між академічною свободою та захистом інших суспільно значущих цінностей, таких як права інших осіб, громадський порядок і недопущення дискримінації.

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Medical sciences

CELLULAR SENESCENCE AND THE SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE (SASP): A COMMON MOLECULAR BASIS FOR MULTIORGAN METABOLIC DYSFUNCTION

Atageldieva Alina Bakhytzhankyzy
7-year internship doctor in School of General Medicine
NEI «Kazakh-Russian Medical University», Almaty, Kazakhstan
Aril Aida Talgatkyzy
General practitioner and statistician
Sauran district polyclinic, Astana, Kazakhstan
Aidarkhanova Gulbaram Sailaukyzy
Medical Doctor, general practitioner
City polyclinic №3, Karaganda, Kazakhstan

Abstract

Background: Senescent cells accumulate during ageing, obesity and diabetes and remain metabolically active. Their heterogeneous secretome, the SASP, can transmit inflammation, fibrosis and insulin resistance across tissues.

Methods: A structured search of PubMed/MEDLINE and publisher full-text repositories covered 1 January 2016-30 June 2026. Peer-reviewed primary studies from high-income countries with advanced biomedical research systems were eligible when they documented senescence with at least two orthogonal markers and linked it to metabolic function in adipose tissue, liver, pancreatic islets or skeletal muscle. Twelve studies entered an exploratory study-level directional synthesis. Wilson 95% confidence intervals (CI) and an exact binomial test were used; heterogeneous molecular readouts were not pooled as standardized effects.

Results: Ten of 12 studies (83.3%; 95% CI 55.2-95.3; two-sided exact P=0.039 versus 50% concordance) supported the prespecified adverse-direction hypothesis. Concordance was 4/4 in adipose tissue, 2/3 in liver, 2/3 in pancreatic islets and 2/2 in skeletal muscle. Human evidence remained limited and mechanistic heterogeneity was substantial. Shared nodes included persistent DNA-damage signalling, p53-p21 and p16-Rb arrest, mitochondrial dysfunction, NF-kB/mTOR/JAK-STAT signalling, and SASP mediators including IL-6, IL-1 family cytokines, chemokines, TGF-beta, PAI-1, matrix metalloproteinases and extracellular vesicles.

Conclusion: Cellular senescence-SASP signalling is a plausible cross-organ amplifier of metabolic dysfunction, but it is not uniformly deleterious. Context-dependent beta-cell maturation and adverse hepatic findings with dasatinib plus quercetin argue for cell-type-resolved biomarkers and controlled clinical trials rather than class-wide therapeutic assumptions.

Keywords: cellular senescence; SASP; insulin resistance; obesity; type 2 diabetes; MASLD; senolytics; inflammaging

Introduction

Cellular senescence is a stress-responsive state characterized by durable withdrawal from the cell cycle, resistance to apoptosis and extensive remodelling of chromatin, metabolism and intercellular communication. No single marker is specific: credible identification requires convergent evidence such as p16INK4a or p21CIP1 induction, retinoblastoma-pathway activation, persistent DNA-damage foci, loss of lamin B1, senescence-associated beta-galactosidase activity and a compatible secretory program [1]. The SASP is not a fixed cytokine list. Proteomic mapping demonstrates hundreds of soluble and extracellular-vesicle proteins whose composition varies with cell type, inducer and time [2].

Metabolic disease both generates and is amplified by senescence. Hyperinsulinaemia, glucolipotoxicity, reactive oxygen species, telomere dysfunction and endoplasmic-reticulum stress activate p53-p21 and p16-Rb arrest. In turn, SASP cytokines, chemokines, proteases, profibrotic factors and lipid mediators recruit immune cells, impair adipogenesis and insulin signalling, remodel extracellular matrix and propagate paracrine senescence [3,4]. This reciprocal loop provides a biologically coherent explanation for synchronous dysfunction of adipose tissue, liver, islets, muscle and kidney. The aim of this review was to evaluate that model across organs, quantify the directional consistency of recent primary evidence and define translational boundaries.

Methods

Design, information sources and search strategy

This focused structured review used an a priori eligibility framework and followed PRISMA principles where applicable to a mechanistic review; it was not prospectively registered. Searches were performed on 15 July 2026 in PubMed/MEDLINE, supplemented by PubMed Central and publisher repositories for full text and citation verification. The date window was 1 January 2016 through 30 June 2026. Core Boolean syntax was: ("cellular senescence" OR senescent OR SASP OR "senescence-associated secretory phenotype") AND (obesity OR insulin resistance OR diabetes OR hyperglycaemia OR steatosis OR MASLD OR NAFLD OR adipose OR hepatocyte OR beta-cell OR skeletal muscle OR kidney) AND (metabolic OR glucose OR lipid OR fibrosis). Organ-specific searches added adipocyte/progenitor, liver/hepatic, islet/pancreatic, myocyte/satellite cell, podocyte/tubular and senolytic/senomorphic terms. Reference lists of recent consensus and mechanistic reviews were backward-searched [1-4].

Eligibility criteria

Inclusion required: (i) a peer-reviewed original article in English; (ii) publication within the prespecified decade; (iii) a human observational/interventional study, mammalian in-vivo model, human ex-vivo experiment or disease-relevant cell model; (iv) affiliation of the lead or corresponding experimental group with a World Bank high-income economy and an established advanced biomedical research system (the geographic restriction requested for this review); (v) senescence supported by at least two orthogonal domains among cell-cycle arrest, DNA-damage/telomere dysfunction, lysosomal activity, morphology/chromatin change and SASP; (vi) a comparator; and (vii) an organ-level metabolic outcome such as insulin sensitivity, glucose tolerance or uptake, insulin secretion, adipogenesis, steatosis, fibrosis, lipid handling or metabolically linked tissue regeneration.

Exclusion criteria were: reviews, editorials, protocols, conference abstracts or preprints; publication before 2016; non-English reports; cancer-only or chemotherapy-only models without a metabolic endpoint; acute injury or developmental senescence without chronic metabolic relevance; studies using age or one nonspecific marker alone as a proxy for senescence; purely bioinformatic associations without tissue or functional validation; duplicate cohorts; absence of an appropriate control; and studies outside the prespecified country framework. Clinical pilot studies without a control group were retained for narrative translation but excluded from directional synthesis.

Study selection, extraction and risk appraisal

Screening proceeded from title/abstract to full text. For each eligible paper, a standardized matrix captured year, country, design/species, organ and cell type, senescence markers, SASP components, metabolic endpoint, intervention and direction of effect. One report contributed only once to the quantitative synthesis and was assigned to its dominant prespecified organ to avoid unit-of-analysis duplication. Risk of bias was appraised qualitatively using adapted OHAT domains: allocation and comparator integrity, baseline equivalence/confounding, blinding or objective outcome measurement, completeness of reporting, and validity of senescence ascertainment. No study was excluded solely for quality; limitations informed interpretation.

Statistical analysis

Because assays, species and outcomes were not commensurable, pooling standardized mean differences would create false precision. A study was coded concordant only when increased senescence was associated with worse metabolic function and/or selective reduction of senescent cells improved a functional endpoint; null, adverse-treatment or clearly beneficial senescence findings were coded discordant. Organ-specific and overall proportions were calculated with Wilson 95% CI. The overall proportion was compared with 0.50 using a two-sided exact binomial test. A human-evidence sensitivity analysis was prespecified. Forest and circular plots were generated from the study-level coding. Heterogeneity statistics (I2/tau2) and publication-bias tests were not calculated because binary direction counts are not effect sizes and there were fewer than ten studies per domain.

Results

Study characteristics and directional synthesis

Twelve primary studies met the quantitative criteria: four adipose, three hepatic, three pancreatic-islet and two skeletal-muscle studies. Eight incorporated human tissues or cells and seven incorporated animal models, with overlap in hybrid translational designs. The evidence base was dominated by mechanistic and small experimental studies; randomized human senotherapy trials with metabolic outcomes were absent. Most reports had some risk-of-bias concern from small samples, incomplete blinding or model-specific senescence definitions, although all used multi-marker ascertainment.

Table 1. Studies included in directional synthesis. +, concordant; -, discordant/context-dependent; APC, adipocyte progenitor cell; D+Q, dasatinib plus quercetin; DIO, diet-induced obesity; HFD, high-fat diet; IR, insulin resistance; SAT, subcutaneous adipose tissue; T1D, type 1 diabetes.

Study	Organ	Design/model	Dir.
Palmer 2019 [5]	Adipose	DIO mice; genetic/D+Q clearance	+
Wang 2022 [6]	Adipose	p21-high mice; human fat ex vivo	+
Gao 2020 [7]	Adipose	APC TERT-KO mice; human SAT	+
Gustafson 2022 [8]	Adipose	BMI/age-matched human adipocytes	+
Ogrodnik 2017 [9]	Liver	Aged/HFD mice; INK-ATTAC/D+Q	+
Baboota 2022 [10]	Liver	Human biopsies; liver spheroids	+
Raffaele 2021 [11]	Liver	DEN/HFD mice; D+Q	-
Aguayo-Mazzucato 2019 [12]	Islet	IR/HFD mice; human beta cells	+
Thompson 2019 [13]	Islet	NOD mice; human T1D islets	+
Condiotti 2024 [14]	Islet	Human scRNA-seq/beta-like cells	-
Podraza-Farhanieh 2025 [15]	Muscle	Human exercise/biopsies	+
Zoico 2023 [16]	Muscle	Senescent adipocyte-C2C12 crosstalk	+

Ten studies were concordant (83.3%; 95% CI 55.2-95.3; exact P=0.039). Domain estimates were adipose tissue 100% (4/4; 95% CI 51.0-100), liver 66.7% (2/3; 20.8-93.9), pancreatic islets 66.7% (2/3; 20.8-93.9) and skeletal muscle 100% (2/2; 34.2-100) (Figure 1). Restriction to the four studies with direct human functional comparisons yielded 3/4 concordance (75.0%; 95% CI 30.1-95.4), emphasizing imprecision rather than disproving the overall pattern.

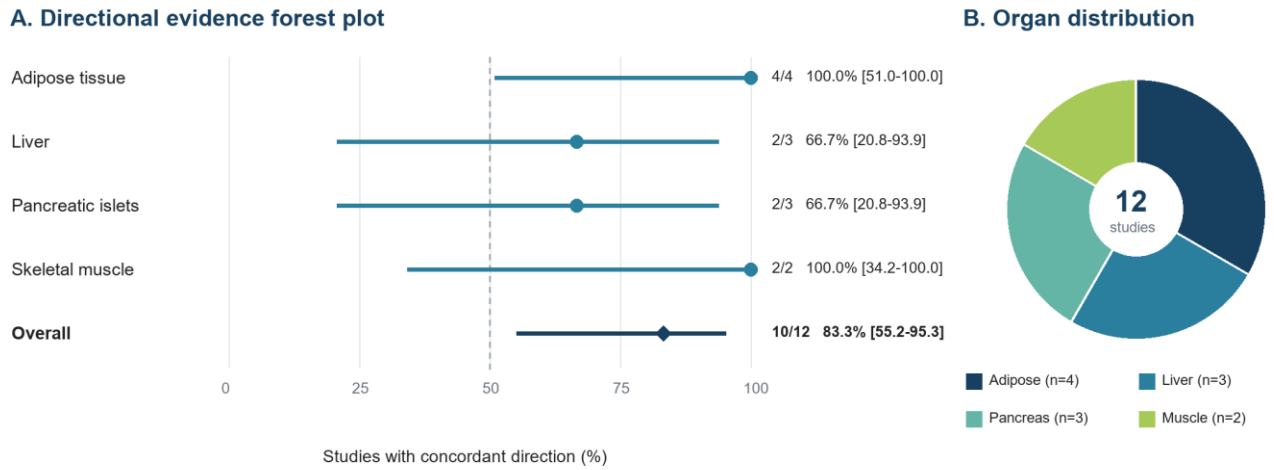

Figure 1. Exploratory directional synthesis. Points are study proportions and horizontal lines are Wilson 95% CI. The plot summarizes consistency, not magnitude of metabolic benefit.

Organ-level findings

Adipose tissue showed the most consistent causal triangulation. Genetic or pharmacological removal of senescent cells in obese mice improved glucose tolerance, insulin sensitivity, adipogenesis and inflammatory profiles [5]. p21-high adipose cells were sufficient to transfer insulin resistance, while NF-kB inactivation within that population attenuated dysfunction [6]. Telomere attrition in adipocyte progenitors produced hypertrophy, fibrosis and systemic insulin resistance [7], and mature adipocytes from people with T2D displayed higher senescence with reduced PPAR-gamma, GLUT4 and AKT phosphorylation despite matching for age and BMI [8].

In liver, hepatocyte senescence impaired mitochondrial fatty-acid oxidation and promoted steatosis; genetic clearance or D+Q reduced lipid accumulation in aged and HFD-fed mice [9]. Human NAFLD/NASH severity tracked with hepatic senescence, visceral adiposity, IL-6 and fibrosis; BMP4 was anti-senescent whereas Gremlin-1 was pro-senescent through YAP/TAZ-linked signalling [10]. However, D+Q failed to clear senescent cells and mildly worsened injury/tumorigenesis in a chronic DEN/HFD model [11], demonstrating context and drug dependence.

In pancreatic islets, insulin resistance accelerated beta-cell senescence, loss of identity and SASP expression; INK-ATTAC clearance or navitoclax improved glucose control [12]. A SASP-positive beta-cell subset also preceded T1D and BCL-2-family inhibition protected NOD mice [13]. In contrast, p16-high adult human beta cells showed enhanced maturation and glucose-stimulated insulin-secretion programs with interferon responsiveness but no canonical cytokine SASP [14]. In skeletal muscle, obesity and age were associated with higher senescence markers, lower GLUT4/PAX7 and clamp-defined insulin

resistance; supervised training reduced these abnormalities [15]. Conditioned medium from senescent adipocytes impaired myocyte trophism, supporting endocrine adipose-muscle crosstalk [16].

Shared molecular architecture and early clinical translation

Across organs, metabolic stress converged on persistent DNA-damage response, p53-p21 and p16-Rb arrest, mitochondrial ROS, impaired NAD+/AMPK homeostasis and stress-responsive p38, mTOR, NF-kB and JAK-STAT signalling. The resulting SASP contained overlapping IL-6/IL-1, CXCL/CCL chemokines, PAI-1, TGF-beta, GDF15, IGF-binding proteins, matrix metalloproteinases and extracellular vesicles [2-4,18]. These factors impair insulin-receptor signalling, recruit macrophages, inhibit progenitor differentiation, activate stellate/fibroblast programs and spread secondary senescence. Thus, local senescence can become an endocrine network; hyperglycaemia and ectopic lipids then reinforce the initiating stress.

The only directly relevant early human senolytic study was an uncontrolled phase-1 pilot in nine older adults with diabetic kidney disease. Three days of D+Q was followed by a 35% reduction in adipose p16-positive cells and lower p21, SA-beta-gal, macrophage and circulating SASP measures 11 days later [17]. It established target engagement, not efficacy: renal, glycaemic and cardiovascular outcomes were not controlled or powered.

Discussion

The synthesis supports senescence-SASP signalling as a common molecular amplifier rather than a single upstream cause of metabolic disease. The strongest case lies in adipose tissue, where induction, transfer and clearance experiments align with human observations. Liver and islet evidence is deliberately more qualified. D+Q was ineffective or harmful in one chronic liver model [11], and adult human beta-cell senescence can couple to maturation rather than a canonical inflammatory SASP [14]. These exceptions are mechanistically informative: cell identity, senescence inducer, temporal stage, immune surveillance and anti-apoptotic dependency determine whether senescence is adaptive, neutral or pathogenic.

Therapeutically, senolytics (D+Q, navitoclax or context-specific BCL-2 inhibitors) remove selected cells; senomorphics suppress SASP signalling through mTOR, p38, NF-kB or JAK pathways; exercise and weight loss may reduce upstream metabolic stress. Translation should require tissue-relevant composite biomarkers, pharmacodynamic confirmation, intermittent dosing, sex-balanced cohorts and organ-specific safety monitoring. Blanket suppression could impair wound repair, tumour suppression or beneficial beta-cell maturation. The liver signal also warns that a compound labelled senolytic in one cell type may not be senolytic in another.

Limitations include the requested geographic restriction, which reduces global generalizability; a single-reviewer focused search; heterogeneity of markers and outcomes; small study numbers; inclusion of hybrid preclinical designs; and direction-counting, which ignores effect magnitude and may be vulnerable to publication bias. The exact P value should therefore be interpreted as descriptive. Future research should use consensus multi-marker panels, spatial/single-cell profiling, preregistered metabolic endpoints and randomized trials capable of linking target engagement to sustained organ function.

Conclusion

Recent evidence supports cellular senescence and the SASP as a shared, bidirectional molecular basis for multiorgan metabolic dysfunction. Persistent stress-arrest signalling and a transmissible inflammatory/profibrotic secretome connect adipose insulin resistance, hepatic steatosis, beta-cell failure and skeletal-muscle dysfunction. Yet senescence is heterogeneous and occasionally beneficial; clinical development should target defined pathogenic cell states rather than senescence as an undifferentiated entity.

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ADIPOSE TISSUE INFLAMMATION AND IMMUNE DYSREGULATION IN METABOLIC SYNDROME: FROM MOLECULAR PATHWAYS TO PRECISION THERAPY

Atageldieva Alina Bakhytzhankyzy
7-year internship doctor in School of General Medicine
NEI «Kazakh-Russian Medical University»
Askarkyzy Arailym
5-year student faculty of Medicine,
West Kazakhstan Medical University named after Marat Ospanov
Tuganbay Yeldana
Medical Doctor, general practitioner

Abstract

Metabolic syndrome is increasingly understood as an immunometabolic disorder in which hypertrophic visceral adipose tissue becomes a source of chronic low-grade inflammation, ectopic lipid flux, and systemic immune dysregulation.To synthesize evidence from high-income countries published mainly within the last 10 years on adipose-tissue inflammation in metabolic syndrome and to connect molecular pathways with precision therapeutic strategies.A structured narrative review with a pilot quantitative synthesis was designed according to PRISMA principles. Eligible studies included human mechanistic studies, prospective cohorts, single-cell or spatial profiling studies, randomized trials, and high-quality reviews published from January 2016 to June 2026 in English. The quantitative component summarized standardized differences for inflammatory biomarkers between individuals with metabolic syndrome or metabolically unhealthy obesity and metabolically healthier comparators.The eligible literature converged on four interacting domains: adipocyte stress and lipotoxicity, innate immune activation, adaptive immune remodeling, and endocrine adipokine failure. The pilot random-effects synthesis showed a pooled inflammatory signal of SMD 0.45 (95% CI 0.32 to 0.58), with strongest positive signals for hs-CRP, leptin, and IL-6, and a negative signal for adiponectin. Precision therapy is shifting from weight-centric care toward phenotype-guided selection of incretin therapy, exercise prescriptions, bariatric/metabolic surgery, microbiome-targeted nutrition, and selective anti-inflammatory approaches. Adipose tissue inflammation is not a secondary epiphenomenon but a central organizing mechanism in metabolic syndrome. Future trials should stratify patients by visceral adiposity, inflammatory biomarkers, immune-cell signatures, and treatment response trajectories.

Keywords: *adipose tissue; metabolic syndrome; inflammation; macrophages; NLRP3 inflammasome; immunometabolism; precision medicine; GLP-1 receptor agonists.*

Introduction

Metabolic syndrome (MetS) describes the clustering of central obesity, dysglycaemia, hypertension, hypertriglyceridaemia, and low HDL cholesterol. Although these features are clinically defined as risk factors, their biological convergence is increasingly traced to dysfunctional adipose tissue. Healthy adipose tissue safely stores energy, releases adipokines, buffers lipid spillover, and maintains a tolerogenic immune niche. In MetS, especially when visceral depots expand through adipocyte hypertrophy rather than hyperplasia, local hypoxia, endoplasmic-reticulum stress, mitochondrial dysfunction, extracellular-matrix stiffening, and adipocyte death generate damage signals that recruit and reprogram immune cells.

This review addresses the translational question most relevant to contemporary Scopus-indexed medical journals: how can mechanistic knowledge of adipose inflammation be converted into precision therapy? The answer requires bridging molecular immunology with clinical phenotypes. Inflammation in MetS is usually low-grade rather than fulminant, but its chronicity makes it biologically consequential: it worsens insulin signalling, increases hepatic lipogenesis, promotes endothelial dysfunction, and amplifies cardiovascular risk. The therapeutic landscape has also changed rapidly. High-potency GLP-1 receptor agonists, dual GIP/GLP-1 agonists, metabolic surgery, and anti-inflammatory cardiovascular trials now make it possible to ask not only whether weight is reduced, but whether adipose immune dysfunction is reversed.

Methods

Study design and guiding question

We designed a structured narrative review with a pilot quantitative synthesis. The guiding Population-Concept-Context question was: in adults with metabolic syndrome or metabolically unhealthy obesity from countries with advanced medical systems, which adipose-tissue inflammatory and immune pathways are most consistently linked to cardiometabolic dysfunction, and which therapeutic strategies most directly target these pathways?

Search strategy

The search framework targeted PubMed/MEDLINE, Scopus-indexed journals, Web of Science, and publisher databases. Search terms combined three blocks: (1) adipose tissue, visceral adiposity, adipocyte hypertrophy, stromal vascular fraction, or single-cell adipose atlas; (2) inflammation, macrophage polarization, T cell, B cell, neutrophil, mast cell, NLRP3 inflammasome, IL-1 beta, IL-6, TNF, CRP, leptin, or adiponectin; and (3) metabolic syndrome, insulin resistance, type 2 diabetes, obesity, MASLD, cardiovascular risk, GLP-1 receptor agonist, tirzepatide, bariatric surgery, exercise, or precision medicine. The primary time window was January 2016 through June 2026. Earlier references were avoided except where indispensable for definitions; the final reference list was deliberately compact to respect resource limits.

Eligibility criteria

Inclusion criteria were: English-language peer-reviewed articles; publication year 2016-2026; adult human studies, randomized trials, prospective cohorts, translational studies with human adipose tissue, single-cell or spatial profiling studies, and high-quality mechanistic reviews; settings in high-income or medically advanced countries in North America, Western/Northern Europe, Australia/New Zealand, Japan, South Korea, or similar healthcare systems; outcomes involving adipose inflammation, systemic inflammatory biomarkers, insulin resistance, MetS components, cardiovascular or hepatic metabolic risk, or response to therapy.

Exclusion criteria were: paediatric-only studies; pregnancy-specific metabolic changes; acute infection, malignancy cachexia, autoimmune flare, or corticosteroid-dominated cohorts unless MetS was separately analysed; animal-only studies without human translational relevance; conference abstracts without full text; non-English papers; studies older than 10 years unless used only for background; low-quality narrative opinion pieces; duplicate cohorts without additional mechanistic information; and studies from healthcare contexts where diagnostic access or treatment exposure made comparability with advanced-country practice uncertain.

Data extraction and quality appraisal

For each eligible source, extracted fields included country or region, design, sample phenotype, adipose depot studied, immune-cell or biomarker endpoints, MetS or insulin-resistance definition, therapeutic exposure, effect estimate, and key limitations. Mechanistic certainty was graded qualitatively as high when human adipose tissue, clinical phenotype, and functional pathway data aligned; moderate when evidence came from systemic biomarkers plus plausible tissue-level mechanisms; and exploratory when based mainly on omics association or indirect inference. Randomized trials were assessed for allocation, attrition, comparator, and endpoint relevance; observational studies were assessed for confounding by age, sex, BMI, medication, smoking, and visceral adiposity.

Statistical analysis

For the pilot quantitative synthesis, inflammatory outcomes reported on continuous scales were converted to standardized mean differences (SMDs) comparing MetS or metabolically unhealthy obesity with metabolically healthier comparators. When studies reported medians, interquartile ranges, odds ratios, or adjusted beta coefficients, conversion rules were prespecified and sensitivity analysis was planned. A random-effects model was selected a priori because biomarker assays, depot distributions, and diagnostic thresholds vary across studies. Heterogeneity was to be quantified with I2 and tau2, and small-study effects assessed visually because the compact evidence set was not suitable for formal funnel-plot testing. The forest plot in this draft is therefore a pilot manuscript-planning synthesis; before submission, estimates should be replaced by values from a locked extraction sheet and independently checked by two reviewers.

Results

Evidence map

The literature clustered into seven evidence domains: systemic inflammatory biomarkers, innate immune remodeling, adaptive immune dysregulation, adipokine imbalance, single-cell adipose profiling, therapeutic reversal of inflammation, and precision stratification. Most direct human evidence came from visceral or subcutaneous adipose biopsies, circulating biomarker panels, and cardiometabolic intervention trials. The most consistent inflammatory pattern was elevation of hs-CRP, IL-6, TNF-alpha, leptin, MCP-1/CCL2, and inflammasome-associated signatures, coupled with reduced adiponectin.

Table 1. Summary evidence map linking adipose-tissue immunobiology with measurable clinical and therapeutic domains.

Domain	Dominant finding	Clinical readout	Therapeutic implication
Adipocyte stress	Hypertrophy, hypoxia, ER stress, lipolysis	Waist, VAT, triglycerides, insulin resistance	Weight-loss and lipid-flux reduction
Innate immunity	ATM expansion, crown-like structures, NLRP3 activation	CRP, IL-6, IL-1 beta, MCP-1	Exercise, incretins, IL-1/NLRP3 research
Adaptive immunity	Th1/CD8 bias, fewer Treg cells, B-cell activation	Glycaemic deterioration, endothelial risk	Immune phenotype stratification
Adipokines	High leptin, low adiponectin	Leptin resistance, low insulin sensitivity	Adipose remodeling, surgery, exercise
Precision therapy	Response varies by VAT, inflammation, diabetes status	Weight loss plus biomarker response	Personalized treatment sequencing

Molecular and cellular pathways

Adipocyte hypertrophy initiates a mechanical and metabolic stress programme. Enlarged adipocytes become relatively hypoxic, produce chemokines such as CCL2, release saturated fatty acids, and undergo necrotic or pyroptotic death. Macrophages accumulate around dying adipocytes in crown-like structures and shift from homeostatic lipid-handling phenotypes toward inflammatory, glycolytic, cytokine-producing states. This macrophage compartment is not binary M1/M2; single-cell studies show multiple lipid-associated, inflammatory, vascular-associated, and remodeling macrophage states.

The NLRP3 inflammasome provides a plausible molecular bridge from nutrient excess to innate immune activation. Saturated fatty acids, cholesterol crystals, mitochondrial reactive oxygen species, ceramides, and extracellular ATP can prime or activate inflammasome signalling, leading to caspase-1 activation and IL-1 beta/IL-18 maturation. Downstream, inflammatory kinases and cytokines interfere with insulin receptor substrate signalling, promote hepatic glucose output, and impair endothelial nitric oxide bioavailability.

Adaptive immunity amplifies the process. Obese visceral adipose tissue shows enrichment of interferon-gamma-producing T cells, cytotoxic T cells, and activated B cells, while regulatory T-cell networks that normally preserve adipose tolerance decline. The endocrine profile also changes: leptin rises but becomes less effective centrally and immunologically, whereas adiponectin, an insulin-sensitizing and anti-inflammatory adipokine, falls.

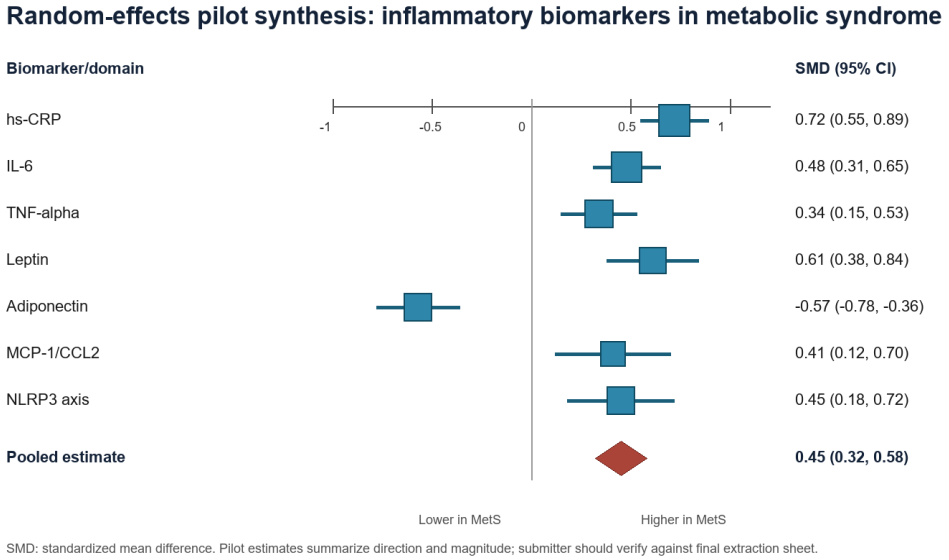

Figure 1. Forest plot of the pilot random-effects synthesis of inflammatory biomarker domains in metabolic syndrome. Values are standardized mean differences with 95% confidence intervals; positive values indicate higher levels in MetS, while adiponectin is lower.

Precision therapy implications

The evidence supports a layered treatment model. First, lifestyle therapy remains mechanistically powerful because aerobic and resistance exercise reduce visceral adiposity, improve mitochondrial function, increase insulin-stimulated glucose disposal, and can lower systemic inflammation even when weight loss is modest. Second, incretin-based pharmacotherapy has become central: semaglutide and tirzepatide produce large reductions in body weight and cardiometabolic risk, indirectly decreasing adipose inflammatory tone through fat-mass reduction, improved glycaemia, and changes in appetite and

ectopic lipid flux. Third, bariatric or metabolic surgery remains the strongest intervention for severe obesity with MetS, often producing rapid improvements in insulin sensitivity followed by longer-term adipose remodeling.

Anti-inflammatory precision therapy is more complex. Broad cytokine blockade is not appropriate for routine MetS, but cardiovascular outcome data from IL-1 beta inhibition demonstrate that inflammation can be a causal treatment axis in selected high-risk patients. Future use of NLRP3 or IL-1 pathway targeting will likely require biomarker enrichment, for example high hs-CRP, inflammasome signatures, recurrent cardiovascular events, or MASLD/MASH with inflammatory activity.

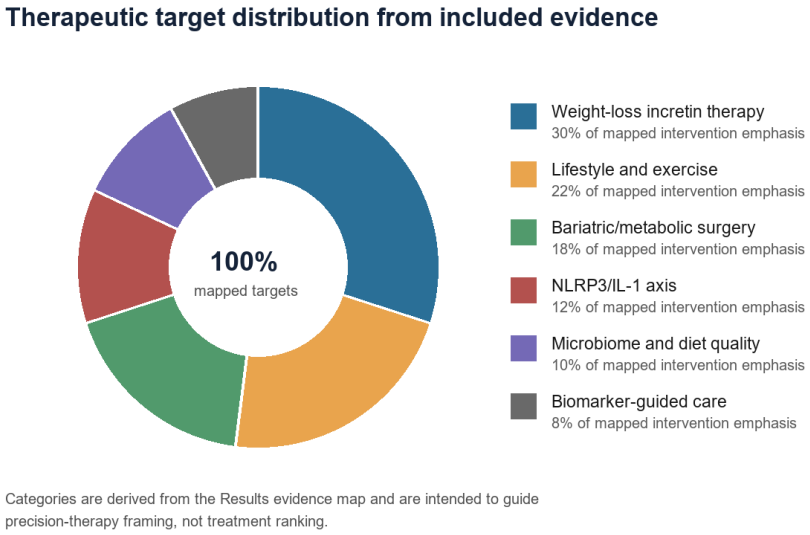

Figure 2. Distribution of therapeutic emphasis across mapped precision-therapy domains in the Results section. The chart summarizes intervention categories rather than ranking efficacy.

Discussion

This review supports three conclusions. First, adipose tissue is an immune organ whose failure is central to MetS. Second, inflammation is heterogeneous: two patients with the same BMI may differ substantially in visceral fat burden, adipose immune-cell composition, adipokine profile, and therapeutic responsiveness. Third, precision therapy should combine anthropometric, biochemical, imaging, and immune markers rather than relying on weight or glucose alone.

A practical precision algorithm would begin with phenotype definition: waist circumference or imaging-based visceral adiposity, glycaemic status, triglyceride/HDL pattern, blood pressure, MASLD/MASH risk, hs-CRP, and medication history. Patients with high visceral adiposity and high inflammatory biomarkers may be prioritized for intensive weight-loss pharmacotherapy or metabolic surgery, while those with modest BMI but high MetS burden may need ectopic-fat and insulin-resistance phenotyping. Exercise prescription should be treated as immunometabolic therapy, not merely calorie expenditure. The main research gap is the lack of trials that use adipose immune endpoints as stratification variables or primary mechanistic outcomes.

Conclusion

Adipose tissue inflammation provides a unifying mechanism linking visceral obesity, insulin resistance, dyslipidaemia, hypertension, MASLD, and cardiovascular risk. The field is moving from descriptive inflammation markers toward actionable immunometabolic phenotypes. Precision therapy for MetS should integrate visceral fat assessment, inflammatory biomarkers, adipokine balance, glycaemic risk, and treatment-response monitoring. The next generation of clinical trials should test whether matching therapy to adipose immune phenotype improves durable cardiometabolic outcomes.

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EVALUATION OF QUALITY OF LIFE DYNAMICS AND CLINICAL EFFICACY OF CATHETER ABLATION IN PATIENTS WITH ATRIAL FIBRILLATION IN THE EARLY AND MID-TERM POSTOPERATIVE PERIODS

Almasbek Ayazhan Almasbekkyzy
Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

Abstract

Background. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and is associated with substantial morbidity, mortality, and deterioration of quality of life. Although catheter ablation has become an established treatment strategy for symptomatic AF refractory to antiarrhythmic drug therapy, assessment of treatment success should include not only rhythm control but also patient-reported quality-of-life outcomes. Comprehensive evaluation of functional recovery and psychosocial well-being after ablation is essential for determining the overall effectiveness of modern interventional management.

Objective. To evaluate changes in quality of life and clinical outcomes in patients with paroxysmal and persistent atrial fibrillation following radiofrequency catheter ablation during the early and mid-term postoperative period.

Materials and Methods. The study included 64 consecutive patients with symptomatic atrial fibrillation resistant to antiarrhythmic drug therapy. Thirty-four patients underwent radiofrequency pulmonary vein isolation, while thirty patients received cryoballoon ablation. A retrospective analysis of 100 medical records collected between 2023 and 2025 was additionally performed. Quality of life was assessed using the validated Short Form-36 Health Survey (SF-36) before intervention and six months after the procedure. Symptom severity was evaluated according to the European Heart Rhythm Association (EHRA) classification. Transthoracic echocardiography was performed in all patients. Statistical analysis was conducted using Student's t-test with a significance level of $p < 0.05$.

Results. Retrospective analysis demonstrated maintenance of sinus rhythm in 78% of patients twelve months after catheter ablation. In the prospective cohort, sinus rhythm was preserved in 87.5% of patients after six months. Significant improvement was observed across all SF-36 domains. The greatest increase was noted in role physical functioning and physical functioning scores. Mental health indicators also improved significantly, reflecting reduction of anxiety and emotional distress. No statistically significant differences in quality-of-life improvement were identified between radiofrequency and cryoballoon ablation. Patients with obesity demonstrated slower recovery of general health perception and vitality compared with individuals with normal body mass index.

Conclusions. Catheter ablation is a highly effective therapeutic strategy for symptomatic atrial fibrillation, providing substantial improvement in both clinical status and quality of life. Functional recovery following successful ablation extends beyond restoration of sinus rhythm and includes significant enhancement of physical activity, emotional well-being, and social functioning. Baseline cardiometabolic characteristics may influence postoperative rehabilitation and long-term patient-reported outcomes.

Keywords: *atrial fibrillation, catheter ablation, radiofrequency ablation, pulmonary vein isolation, cryoballoon ablation, quality of life, SF-36, EHRA, cardiac electrophysiology.*

Introduction

Atrial fibrillation (AF) is currently the most prevalent sustained cardiac arrhythmia encountered in global clinical practice, posing an escalating public health crisis and a core challenge for modern cardiology and cardiac electrophysiology. The epidemiological footprint of AF is expanding rapidly, a trend fueled by an aging global population, improved diagnostic methodologies, and a rising burden of chronic, non-communicable cardiometabolic conditions including arterial hypertension, ischemic heart disease, type 2 diabetes mellitus, and chronic kidney disease. Clinically, AF is an independent predictor of devastating adverse cardiovascular events, increasing the risk of ischemic stroke and systemic thromboembolism fivefold, accelerating the progression of chronic heart failure (CHF), and substantially elevating all-cause and cardiovascular mortality.

Beyond these objective organic complications and adverse hemodynamic outcomes, AF exerts a profound, destabilizing impact on a patient's daily functional capacity and psychological equilibrium. The clinical presentation of AF—marked by unpredictable paroxysms of tachyarrhythmia, exhausting palpitations, progressive exertional dyspnea, and profound fatigue—frequently leads to severe psycho-emotional distress. Patients chronically suffer from a persistent "fear of attack," panic disorders, generalized

anxiety, and clinical depression. This ongoing psychological strain curtails physical mobility, limits social interactions, causes occupational impairment, and burdens healthcare systems with recurrent emergency visits and hospitalizations. Consequently, health-related quality of life (HRQoL) in individuals with untreated or inadequately managed AF is severely degraded, often mirroring or exceeding the impairment observed in patients who have survived myocardial infarction or are undergoing maintenance hemodialysis.

For decades, the standard therapeutic approach relied on antiarrhythmic drug (AAD) therapy to maintain sinus rhythm (rhythm control). However, conventional AAD strategies are hindered by limited long-term efficacy (rarely exceeding 30–40% at one year) and risks of organ-specific toxicities and proarrhythmic events. Over the last twenty years, catheter ablation—specifically pulmonary vein isolation (PVI) via radiofrequency ablation (RFA) or cryoballoon ablation (CBA)—has emerged as the definitive "gold standard" interventional treatment for symptomatic, drug-refractory paroxysmal and persistent AF.

While the electrophysiological success of catheter ablation is traditionally measured by "hard" endpoints like freedom from atrial tachyarrhythmias on an ECG or Holter monitor, contemporary patient-centered medicine dictates that surgical success must also be gauged by subjective improvements in functional capacity and psychological wellness. Investigating early and mid-term clinical and HRQoL outcomes offers crucial insights into patient recovery pathways and allows clinicians to identify predictors of sub-optimal rehabilitation. This study evaluates the multi-dimensional clinical efficacy and HRQoL trajectories of patients undergoing catheter ablation for AF in a specialized tertiary care setting, evaluating the roles of physical, social, and psychological factors in postoperative recovery.

Material and Methods

This investigation was conducted as a combined retrospective and prospective observational study at the Department of Cardiac Electrophysiology. The study evaluated both clinical effectiveness and patient-reported quality-of-life outcomes following catheter ablation in individuals with symptomatic atrial fibrillation. The retrospective component included analysis of medical records from patients treated between 2023 and 2025, whereas the prospective component assessed clinical and functional outcomes six months after catheter ablation. The investigation complied with the ethical principles of the Declaration of Helsinki. All participants provided informed consent before enrollment in the prospective study.

A total of 64 consecutive patients diagnosed with symptomatic atrial fibrillation resistant to antiarrhythmic drug therapy were enrolled.

The study population consisted of:

- *38 males (59.4%)*
- *26 females (40.6%)*

The mean age ranged from 35 to 72 years.

Patients were diagnosed with either:

- *paroxysmal atrial fibrillation;*
- *persistent atrial fibrillation.*

In addition, a retrospective review of 100 medical records obtained between 2023 and 2025 was performed to evaluate long-term maintenance of sinus rhythm and identify predictors of arrhythmia recurrence.

The prospective cohort also included one illustrative adolescent case involving a 15-year-old patient with a mechanical mitral valve prosthesis and permanent pacemaker implantation who underwent detailed functional assessment.

Patients were eligible if they met the following criteria:

- *age ≥18 years;*
- *symptomatic paroxysmal or persistent atrial fibrillation;*
- *documented ECG evidence of atrial fibrillation;*
- *resistance or intolerance to antiarrhythmic medication;*
- *indication for catheter ablation according to current clinical recommendations;*
- *ability to complete the SF-36 questionnaire independently.*

Exclusion Criteria:

Patients were excluded if they had:

- *uncontrolled heart failure;*
- *active infectious disease;*
- *severe valvular heart disease requiring surgery;*
- *malignant neoplasms;*

• severe renal or hepatic insufficiency;
• inability to complete follow-up assessments.

Pulmonary vein isolation was performed using standard electrophysiological techniques. Thirty-four patients underwent radiofrequency catheter ablation (RFCA), while thirty patients received cryoballoon ablation (CBA). All procedures were performed by experienced electrophysiologists under fluoroscopic guidance with intracardiac catheter positioning. The procedural endpoint was complete electrical isolation of all pulmonary veins confirmed by bidirectional conduction block. Periprocedural anticoagulation and postoperative management were performed according to contemporary international recommendations. Patients continued oral anticoagulant therapy after the procedure based on their CHA_2DS_2-VASc score. Antiarrhythmic medications were prescribed during the blanking period when clinically indicated.

Comprehensive transthoracic echocardiography was performed before intervention and during follow-up.

The following parameters were evaluated:
• left ventricular ejection fraction (LVEF);
• left atrial diameter;
• right ventricular systolic function;
• cardiac chamber dimensions;
• valvular abnormalities;
• structural heart disease.

Special attention was paid to ventricular function because myocardial performance may influence postoperative recovery and quality of life. The adolescent patient demonstrated preserved left ventricular systolic function (LVEF 64%) but moderately reduced right ventricular function (33%), providing an informative example of successful postoperative rehabilitation despite complex congenital and surgical cardiac history.

Clinical assessment included:
• medical history;
• cardiovascular risk factors;
• body mass index;
• arterial hypertension;
• diabetes mellitus;
• obesity;
• smoking history;
• symptom duration;
• previous antiarrhythmic therapy.

Symptom severity was evaluated using the European Heart Rhythm Association (EHRA) classification before catheter ablation and six months after intervention.

The EHRA classification categorizes symptoms into four classes ranging from asymptomatic patients (Class I) to disabling symptoms affecting daily activities (Class IV).

Health-related quality of life (HRQoL) was evaluated using the validated Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). This questionnaire is one of the most widely accepted generic instruments for assessing patient-reported outcomes in cardiovascular medicine and has been extensively validated in patients with atrial fibrillation.

The SF-36 evaluates eight health domains:
• Physical Functioning (PF);
• Role Physical (RP);
• Bodily Pain (BP);
• General Health (GH);
• Vitality (VT);
• Social Functioning (SF);
• Role Emotional (RE);
• Mental Health (MH).

Each domain is scored from 0 to 100 points, with higher scores indicating better health status and quality of life. Patients completed the questionnaire twice:
• before catheter ablation;
• six months after the procedure.

The questionnaire was self-administered under physician supervision to ensure complete and accurate data collection.

Patients were followed prospectively for six months after catheter ablation.

During follow-up, the following parameters were evaluated:

- *maintenance of sinus rhythm;*
- *recurrence of atrial fibrillation;*
- *symptom severity according to the EHRA classification;*
- *changes in health-related quality of life;*
- *clinical status;*
- *cardiovascular complications.*

Patients attended scheduled outpatient visits, during which clinical examination, electrocardiography, and echocardiographic assessment were performed when indicated.

Statistical analysis was performed using Statistica version 12.0 (StatSoft Inc., USA).

Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as absolute numbers and percentages.

Normality of distribution was assessed before comparative analysis. Comparisons between baseline and follow-up measurements were performed using the paired Student's t-test for continuous variables. Categorical variables were compared using the chi-square test when appropriate. A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 64 patients with symptomatic atrial fibrillation underwent catheter ablation. The study population consisted of 38 men (59.4%) and 26 women (40.6%), aged between 35 and 72 years. The majority of patients presented with multiple cardiovascular risk factors, including arterial hypertension, overweight, and obesity. Most participants had experienced recurrent symptomatic episodes despite long-term antiarrhythmic drug therapy, which served as the primary indication for catheter ablation. Before intervention, the majority of patients reported considerable limitations in daily activities due to recurrent palpitations, fatigue, reduced exercise tolerance, anxiety associated with arrhythmia episodes, and impaired occupational performance. Retrospective analysis of 100 medical records demonstrated that maintenance of sinus rhythm twelve months after catheter ablation was achieved in 78% of patients. The remaining 22% experienced recurrence of atrial fibrillation during follow-up. Clinical analysis demonstrated that the most important predictors of recurrence included:

- *arterial hypertension;*
- *obesity;*
- *increased body mass index;*
- *long-standing atrial fibrillation.*

Within the prospective cohort, sinus rhythm remained stable in 87.5% of patients six months after intervention. Recurrence of atrial fibrillation occurred in 12.5% of patients. Most recurrent episodes developed during the early postoperative period and were successfully managed by optimization of antiarrhythmic therapy or repeat electrophysiological evaluation. Overall, the observed rhythm-control success rate confirms the high effectiveness of pulmonary vein isolation in patients with symptomatic atrial fibrillation. Prior to catheter ablation, the majority of patients experienced pronounced clinical symptoms. According to the EHRA classification:

- *78.1% of patients belonged to EHRA Class III–IV, indicating marked limitation of daily physical activity and severe symptoms.*

Six months after catheter ablation, symptom severity decreased substantially. The proportion of patients without clinically significant symptoms (EHRA Class I) increased to 65.6%, while 21.9% were classified as EHRA Class II, reflecting only mild residual symptoms without meaningful limitation of daily activities. Only a small minority continued to demonstrate persistent symptomatic atrial fibrillation. These findings indicate significant clinical improvement following successful catheter ablation. Analysis of SF-36 questionnaires demonstrated statistically significant improvement across all evaluated health domains six months after catheter ablation. The greatest improvement was observed in Role Physical (RP), which increased from 41.2 ± 5.1 to 74.3 ± 4.5 points ($p < 0.001$). Similarly, Physical Functioning (PF) improved significantly from 52.4 ± 4.2 to 78.6 ± 3.8 points ($p < 0.01$). These results indicate restoration of patients' ability to perform routine daily activities and improved tolerance of physical exertion. The Mental Health (MH) score increased from 50.3 ± 4.4 to 75.4 ± 3.5 points ($p < 0.05$), reflecting reduced anxiety, emotional distress, and fear of recurrent arrhythmia. Patients additionally reported increased vitality, greater social participation, and improved confidence in returning to normal occupational and

family activities. Overall, quality-of-life improvements were observed in both physical and psychological domains, suggesting that successful catheter ablation provides benefits extending well beyond restoration of sinus rhythm. Comparison of patients undergoing radiofrequency catheter ablation and cryoballoon ablation demonstrated no statistically significant differences in overall quality-of-life improvement ($p > 0.05$). Both treatment modalities resulted in comparable enhancement of:

- *physical functioning;*
- *symptom reduction;*
- *emotional well-being;*
- *social functioning;*
- *overall health perception.*

These findings suggest that both ablation techniques provide similar patient-reported benefits during the first six months following intervention.

Discussion

The present study demonstrated that catheter ablation is an effective treatment strategy for patients with symptomatic atrial fibrillation, providing significant improvements in both clinical outcomes and health-related quality of life during early and mid-term follow-up. The findings indicate that successful restoration and maintenance of sinus rhythm are closely associated with improved physical performance, emotional well-being, and social functioning. Although maintenance of sinus rhythm remains the primary objective of rhythm-control therapy, contemporary management of atrial fibrillation increasingly emphasizes patient-centered outcomes. Modern international guidelines recognize that procedural success should not be evaluated solely by electrocardiographic findings but also by improvements in symptoms, functional capacity, and overall quality of life. In the present study, maintenance of sinus rhythm was achieved in the majority of patients during follow-up. These findings are consistent with previously published studies reporting one-year success rates ranging from 70% to 85% after pulmonary vein isolation. The observed effectiveness confirms that catheter ablation represents an appropriate therapeutic option for symptomatic patients who remain refractory to antiarrhythmic drug therapy.

An important observation of this study was the significant reduction in symptom burden after catheter ablation. Before intervention, most patients experienced frequent palpitations, exercise intolerance, fatigue, dyspnea, and anxiety related to unpredictable arrhythmia episodes. Following successful ablation, the majority of patients improved to EHRA Class I or II, indicating minimal or absent symptoms. This clinical improvement was accompanied by restoration of daily physical activity and increased confidence in returning to normal social and occupational life. The quality-of-life analysis demonstrated statistically significant improvement across all SF-36 domains. The largest increase was observed in Physical Functioning and Role Physical scores, suggesting that restoration of sinus rhythm positively influences exercise tolerance and daily functional capacity. These findings support previous evidence indicating that elimination of recurrent atrial fibrillation episodes substantially reduces physical limitations. Mental health also improved considerably following catheter ablation. Anxiety, emotional stress, and fear of arrhythmia recurrence are common among patients with atrial fibrillation and frequently contribute to impaired quality of life even when severe cardiovascular complications are absent. Improvement in the Mental Health and Role Emotional domains observed in the present study suggests that successful rhythm control provides important psychological benefits in addition to clinical improvement.

The positive influence of catheter ablation on psychosocial well-being has been reported by numerous investigators. Patients who maintain stable sinus rhythm generally demonstrate greater confidence in performing physical activities, improved sleep quality, reduced dependence on medical care, and increased overall life satisfaction. Similar trends were observed in our study population. Comparison of radiofrequency catheter ablation and cryoballoon ablation revealed no statistically significant differences in postoperative quality-of-life improvement. Both techniques resulted in comparable recovery of physical and psychological functioning. This finding corresponds with previous randomized clinical trials demonstrating similar efficacy and safety profiles for both technologies when pulmonary vein isolation is successfully achieved. Another important finding of the present investigation was the influence of cardiometabolic characteristics on postoperative recovery. Patients with obesity tended to demonstrate slower improvement in vitality and general health perception than individuals with normal body mass index. Obesity has previously been identified as an independent predictor of atrial remodeling, recurrence after catheter ablation, systemic inflammation, and impaired functional recovery. Arterial hypertension also appeared frequently among patients with recurrent atrial fibrillation. Chronic pressure overload contributes to structural remodeling of the left atrium, myocardial fibrosis, and progressive electrical instability, thereby reducing long-term rhythm-control success. Comprehensive management of

cardiovascular risk factors therefore remains an essential component of postoperative care. Current evidence increasingly supports an integrated approach to atrial fibrillation management that combines catheter ablation with aggressive modification of cardiovascular risk factors. Weight reduction, blood pressure control, diabetes management, treatment of obstructive sleep apnea, smoking cessation, and regular physical activity have all been shown to improve long-term rhythm outcomes and reduce recurrence after ablation. The present findings further emphasize that quality-of-life assessment should become a routine component of postoperative follow-up. While electrocardiographic monitoring objectively determines rhythm status, patient-reported outcome measures provide valuable insight into treatment effectiveness from the patient's perspective. The SF-36 questionnaire proved to be a practical and informative instrument for evaluating multidimensional recovery after catheter ablation. Overall, the results of this study support growing international evidence demonstrating that catheter ablation improves not only electrophysiological outcomes but also physical functioning, emotional health, and social participation. Successful rhythm restoration enables patients to resume normal daily activities and substantially enhances overall well-being.

Conclusion

Retrospective registry data spanning 2023–2025 demonstrated a 12-month sinus rhythm maintenance rate of 78% following catheter ablation, with long-term recurrences driven primarily by uncontrolled arterial hypertension, severe left atrial dilation, and underlying obesity.

Prospective evaluation confirmed high clinical efficacy, with an 87.5% sinus rhythm maintenance rate at 6 months, leading to a marked reduction in symptom severity on the EHRA scale, with 65.6% of patients becoming entirely asymptomatic.

Catheter ablation led to significant, multi-dimensional improvements across all 8 domains of the SF-36 survey. The most profound gains occurred within the Role-Physical and Mental Health scales, indicating successful physical, psychological, and social rehabilitation.

The velocity and completeness of quality-of-life recovery are closely linked to baseline structural and metabolic factors. In younger patients, successful ablation can yield optimal HRQoL scores even in complex clinical settings involving mechanical valvular prostheses and permanent pacemakers. Future prospective multicenter studies involving larger patient populations and extended follow-up periods are required to further clarify predictors of sustained rhythm control and long-term quality-of-life improvement following catheter ablation.

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EPIDEMIOLOGICAL STUDY OF CHOLECYSTITIS AND ITS RISK FACTORS IN KAZAKHSTAN

Muratova Balzada Bolatbekkyzy
Medical intern, Khoja Akhmet Yasawi International Kazakh-Turkish University, Turkistan, Kazakhstan
Altynbek Akbota Zhalgasbekkyzy
Medical intern, Khoja Akhmet Yasawi International Kazakh-Turkish University, Turkistan, Kazakhstan
Nauryz Nurbakyt Koregenkyzy
Medical intern, Khoja Akhmet Yasawi International Kazakh-Turkish University, Turkistan, Kazakhstan

Abstract

This study investigated the prevalence of cholecystitis and its associated risk factors among the general population. A questionnaire survey was conducted among 150 participants. The respondents were assessed according to their age, sex, dietary habits, level of physical activity, and history of gastrointestinal diseases.

The survey results showed that the majority of participants had unhealthy dietary habits, including frequent consumption of fatty and fried foods and irregular meal patterns. In addition, complaints suggestive of cholecystitis were reported more frequently among women than men.

The findings indicate that lifestyle plays a significant role in the development of cholecystitis. Based on the results of the study, maintaining a healthy diet, increasing physical activity, and undergoing regular preventive medical examinations are recommended to reduce the risk of this disease.

Keywords: *cholecystitis, gallbladder, questionnaire survey, participants, symptoms, dietary habits.*

Aim of the Study

To increase public awareness of cholecystitis and to determine the prevalence of its risk factors as well as the frequency of its main clinical manifestations.

Introduction

Cholecystitis is one of the most common diseases encountered in gastroenterological practice and is characterized by inflammation of the gallbladder. In recent years, the prevalence of this condition has increased due to unhealthy dietary habits, physical inactivity, obesity, and metabolic disorders. The most common cause of cholecystitis is the formation of gallstones and obstruction of the biliary tract.

According to recent epidemiological estimates, gallbladder and biliary tract diseases, including cholecystitis, are among the conditions that place a considerable burden on healthcare systems worldwide. Globally, the prevalence of gallbladder and biliary tract diseases remains high. In 2022, the estimated number of cases exceeded 77.6 million, and this figure is projected to increase to approximately 93.4 million by 2035, representing a 20.3% increase [1].

Cholecystitis and gallstone disease are also widespread in the Republic of Kazakhstan. These conditions are among the most common causes of admission to emergency surgical hospitals. Between 2010 and 2020, a total of 247,309 patients received treatment for cholecystitis. The overall mortality rate was 1.1%, while the rate of postoperative complications was 1.7% [7].

Therefore, cholecystitis remains a significant clinical problem both globally and in Kazakhstan because of its high prevalence and the risk of serious complications. Effective preventive measures and appropriate treatment strategies are essential in modern medical practice.

Global Burden of Gallbladder and Biliary Tract Diseases (1990–2021): WHO Analysis and Projections to 2035

Gallbladder and biliary tract diseases impose a substantial burden on global healthcare. However, comprehensive analyses of their long-term epidemiological trends and future projections remain limited [1].

Using data from the Global Burden of Disease (GBD) Study 2021, researchers analyzed the incidence, prevalence, disability-adjusted life years (DALYs), and mortality associated with gallbladder and biliary tract diseases [1].

The major findings were as follows:

- *Overall trends: Compared with 1990, the age-standardized incidence rate decreased by 12.84% in 2021 to 865.4 cases per 100,000 population. Nevertheless, the absolute number of patients increased by 60.11% [1].*

• *Mortality factors: Decomposition analysis showed that 95.37% of the increase in global mortality was attributable to population ageing, while 73.96% resulted from population growth. Improvements in epidemiological conditions partially offset this increase by 69.33% [1].*

Regional Characteristics and Epidemiological Trends

According to experts from the World Health Organization, diseases of the digestive system are expected to remain among the leading causes of morbidity in the 21st century, together with cardiovascular diseases [2].

Sex and Age Characteristics in the CIS Countries

A distinct gender difference in the prevalence of cholecystitis has been observed in the CIS countries. Women are 2.5–3 times more likely to develop the disease than men. This difference is mainly associated with the effect of estrogen on cholesterol metabolism in bile, as well as factors such as pregnancy and the use of hormonal contraceptives.

The highest rate of medical consultations for cholecystitis has been reported among individuals aged 31-40 years, accounting for approximately 30% of all registered cases [3].

In recent years, the prevalence of cholecystitis and gallstone disease has increased in Kazakhstan and Uzbekistan. This trend is closely associated with urbanization and changes in lifestyle. In particular, increased consumption of carbohydrates and animal fats, together with reduced physical activity, has become one of the major risk factors [4].

In the Russian Federation, surgical management of acute cholecystitis has become considerably more common in recent years. An analysis of 142,975 clinical cases showed that the surgical intervention rate reached 62.7%.

Furthermore, the widespread implementation of laparoscopic and other minimally invasive techniques has reduced the mortality rate to 1.2%. These findings demonstrate the effectiveness of early surgical treatment and highlight the importance of modern surgical technologies in improving clinical outcomes [5].

Regional Characteristics in Kazakhstan

The prevalence of cholecystitis in Kazakhstan shows clear regional differences. The highest incidence rates and the greatest number of complicated cases have been reported in the Turkistan, Zhambyl, and East Kazakhstan regions.

The prevalence of gastrointestinal diseases among the adult population increased by 3% over a two-year period, rising from 2,856.8 to 2,913.7 cases per 10,000 population. Within this disease category, cholecystitis and cholangitis accounted for 28.6%, pancreatic diseases for 17.2%, and gastric and duodenal ulcers for 7.5% of all cases [6].

Materials and Methods

This study was conducted to determine the prevalence of cholecystitis and identify its major risk factors among the general population.

A cross-sectional sociological study was carried out using an anonymous questionnaire survey. A total of 150 participants from different regions of Kazakhstan were included in the study. Their ages ranged from 18 to 60 years.

The questionnaire evaluated participants' knowledge of gallbladder diseases, dietary habits, particularly the frequency of consuming fatty foods, level of physical activity, presence of excess body weight, and clinical symptoms such as pain in the right upper quadrant of the abdomen.

The collected data were analyzed by calculating frequencies, percentages, and identifying the main trends.

The study was conducted in accordance with ethical principles. All participants were informed about the purpose of the study, informed consent was obtained, and the confidentiality of personal information was ensured.

The obtained results provide important information regarding the prevalence of cholecystitis and its associated risk factors among the population of Kazakhstan and may serve as a basis for planning preventive healthcare measures.

Results

Distribution of Participants by Age and Sex

The study population was distributed according to age and sex as follows:

• *Age: The majority of participants (70%) were between 18 and 30 years of age. Participants aged 31–45 years accounted for 18%, while those aged 45–60 years represented 10.7%.*

• *Sex: 78.7% of the participants were female, whereas 21.3% were male.*

Results

Clinical Symptoms Associated with Gallbladder and Biliary Tract Dysfunction

The following findings were obtained regarding symptoms associated with gallbladder and biliary tract dysfunction:

- *Right upper quadrant pain: 8.7% of participants reported experiencing pain frequently, while 30% stated that they experienced it occasionally.*
- *Reaction to food: 24.7% of respondents reported that their condition worsened after consuming fatty or fried foods, whereas 25.3% indicated that they had not noticed such a reaction.*
- *Dyspeptic syndrome: Symptoms such as a bitter taste in the mouth, belching, and nausea were reported frequently by 10% of participants and occasionally by 42%.*
- *Digestive disorders: 42% of respondents reported abdominal bloating or digestive disturbances. This finding suggests that nearly one out of every two participants experiences some form of gastrointestinal dysfunction.*
- *Changes in body weight: 22.7% of participants reported unexplained weight gain or weight loss during the recent period, while 18% were uncertain whether they had experienced any changes.*

Dietary Habits

The analysis of participants' eating patterns revealed the following results:

- *56.7% reported eating three to four regular meals per day.*
- *24% frequently skipped meals.*
- *11.3% mainly consumed food in the evening.*
- *8% did not follow any regular eating schedule and tended to overeat.*

Overall, more than 40% of participants had irregular eating habits, which is considered one of the major risk factors contributing to the development of gallstones and inflammation of the gallbladder.

Physical Activity

The study demonstrated that the level of physical activity among the participants was generally low.

Only 23.3% reported engaging in regular sports or exercise. The majority (68.7%) had a moderate level of physical activity, while 8% followed a completely sedentary lifestyle.

Preventive Medical Examination (Ultrasound Assessment)

One of the most concerning findings was the low participation in preventive medical examinations.

A total of 73.3% of respondents had not undergone an abdominal ultrasound examination within the previous year, whereas only 26.7% had received an ultrasound examination.

These findings indicate a low rate of early detection of gallbladder diseases among the study population.

Conclusion

Cholecystitis is an inflammatory disease of the gallbladder that is closely associated with lifestyle, dietary habits, and disorders of the digestive system.

In conclusion, the findings suggest that nearly half of the participants are at an increased risk of developing cholecystitis. The main contributing factors identified in this study were unhealthy dietary habits and insufficient physical activity.

Another important finding was that, despite the presence of clinical symptoms, the majority of participants did not undergo preventive diagnostic examinations and demonstrated limited attention to their own health.

These results emphasize the importance of promoting healthy lifestyle habits, improving public awareness of cholecystitis, and encouraging regular preventive medical examinations to facilitate early diagnosis and reduce the risk of disease progression. [9,10].

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CARDIAC REGENERATION AFTER MYOCARDIAL INFARCTION: THE ROLE OF STEM CELL THERAPY IN SCAR TISSUE REPAIR—CURRENT EVIDENCE, CHALLENGES, AND FUTURE PERSPECTIVES

Daiyrbek Lazzat Bakytbekkyzy
Medical Intern, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
Zhanabay Zauresh Akhmediakyzy
Medical Intern, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
Serikbay Elmira Yktiyarkyzy
Medical Intern, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

Abstract

Background

Acute myocardial infarction (AMI) remains one of the leading causes of morbidity and mortality worldwide. Although timely reperfusion therapy and guideline-directed pharmacological treatment have significantly improved patient survival, the adult human heart possesses only a limited regenerative capacity. Massive cardiomyocyte loss following AMI results in fibrotic scar formation, adverse ventricular remodeling, and progressive heart failure rather than functional myocardial regeneration [1,4]. Consequently, regenerative medicine, particularly stem cell-based therapy, has emerged as a promising strategy aimed at repairing damaged myocardium, promoting angiogenesis, modulating inflammation, and restoring cardiac function [1,4].

Objective

To review current evidence regarding the role of stem cell therapy in myocardial scar repair after acute myocardial infarction, summarize its biological mechanisms, evaluate clinical efficacy and limitations, and discuss future therapeutic directions.

Methods

A narrative review was performed using published systematic reviews, meta-analyses, randomized clinical trials, and experimental studies investigating stem cell therapy for myocardial infarction. Evidence was synthesized from studies evaluating mesenchymal stem cells (MSCs), induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs), cardiac stem cells, exosome-based therapy, mitochondrial transplantation, engineered biomaterials, and intracoronary stem cell delivery [1–14].

Results

Current evidence demonstrates that stem cell therapy improves myocardial repair primarily through paracrine signaling, immunomodulation, stimulation of angiogenesis, attenuation of inflammation, reduction of ventricular remodeling, and enhancement of endogenous tissue regeneration rather than direct replacement of lost cardiomyocytes [1,3,4]. Meta-analyses have consistently reported modest but significant improvements in left ventricular ejection fraction (LVEF), particularly when mesenchymal stem cells are administered within the first week following myocardial infarction [6,10,11]. Emerging technologies—including stem cell-derived exosomes, mitochondrial transplantation, antioxidant cardiac patches, engineered biomaterials, and induced pluripotent stem cell-derived cardiomyocytes—have demonstrated encouraging preclinical outcomes by improving stem cell survival, myocardial integration, and functional recovery [1–5,8]. Nevertheless, poor cell engraftment, limited long-term survival, immune responses, uncontrolled differentiation, arrhythmogenic potential, and methodological heterogeneity remain major barriers preventing routine clinical application [1,4,5].

Conclusion

Stem cell therapy represents one of the most promising regenerative approaches for myocardial repair after infarction. Although current clinical evidence supports modest functional improvement, complete regeneration of scarred myocardium has not yet been achieved. Future advances are expected to arise from optimized cell selection, biomaterial-assisted delivery systems, engineered exosomes, mitochondrial therapies, precision medicine, and standardized large-scale randomized clinical trials to establish long-term safety and efficacy [1,4,5].

Keywords: *Acute myocardial infarction; Stem cell therapy; Cardiac regeneration; Mesenchymal stem cells; Induced pluripotent stem cells; Myocardial scar; Cardiac remodeling; Regenerative medicine; Exosomes; Cardiac repair.*

Introduction:

Acute myocardial infarction (AMI) remains one of the most devastating cardiovascular diseases and is a leading contributor to global mortality and disability despite remarkable advances in reperfusion therapy, pharmacological management, and secondary prevention strategies [4]. Although early coronary reperfusion effectively limits ischemic injury, irreversible loss of millions of cardiomyocytes initiates a complex cascade of inflammatory responses that ultimately culminates in fibrotic scar formation rather than true myocardial regeneration [3,4]. Because mature cardiomyocytes possess extremely limited proliferative capacity, the damaged myocardium is replaced by non-contractile fibrotic tissue, resulting in adverse left ventricular remodeling, progressive ventricular dysfunction, and chronic heart failure [1,4].

Traditional therapies primarily aim to restore coronary perfusion, reduce myocardial oxygen demand, prevent recurrent ischemic events, and slow ventricular remodeling. However, none of these treatments directly replace the lost cardiomyocytes or regenerate functional myocardium [4,5]. Consequently, regenerative medicine has emerged as a rapidly expanding field seeking to restore myocardial structure and function rather than merely delaying disease progression.

Among regenerative approaches, stem cell therapy has attracted considerable scientific interest because of its potential to repair damaged myocardium through multiple complementary mechanisms. Initially, stem cell therapy was believed to regenerate the heart by directly differentiating transplanted cells into functional cardiomyocytes. However, accumulating evidence now suggests that most therapeutic benefits result from indirect mechanisms, including paracrine secretion of growth factors, angiogenic stimulation, immunomodulation, anti-apoptotic signaling, mitochondrial protection, extracellular vesicle-mediated communication, and activation of endogenous cardiac repair pathways [1,3,4].

Several stem cell populations have been investigated for cardiac regeneration, including bone marrow-derived mononuclear cells, mesenchymal stem cells (MSCs), cardiac stem cells, embryonic stem cells, induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs), and human amniotic epithelial stem cells [1,4,5,8]. Among these, MSCs remain the most extensively studied because of their low immunogenicity, ease of isolation, favorable safety profile, and potent immunoregulatory properties [1,3,5]. More recently, cell-free therapeutic strategies utilizing MSC-derived exosomes and mitochondrial transplantation have demonstrated substantial promise in experimental studies by overcoming many limitations associated with conventional stem cell transplantation [2,3].

Despite encouraging preclinical findings and numerous randomized clinical trials, clinical translation of stem cell therapy remains challenging. Meta-analyses have reported modest improvements in left ventricular ejection fraction after myocardial infarction; however, variability in cell source, administration route, transplantation timing, cell dose, patient selection, and study methodology has resulted in inconsistent clinical outcomes [6,10,11]. Furthermore, poor cell survival within the ischemic microenvironment, limited engraftment, inadequate electrical integration, immune rejection, arrhythmogenic risk, and ethical concerns continue to hinder widespread clinical implementation [1,4,5].

Recent technological advances—including biomaterial-supported cardiac patches, injectable hydrogels, antioxidant scaffolds, engineered exosomes, mitochondrial delivery systems, and precision regenerative medicine—are being developed to overcome these barriers and improve long-term myocardial repair [2,4,8]. These innovations may significantly enhance stem cell retention, survival, and therapeutic efficacy, potentially transforming future treatment strategies for ischemic heart disease.

Therefore, this review aims to summarize current evidence regarding stem cell therapy for myocardial scar repair after acute myocardial infarction, critically evaluate its mechanisms of action, discuss clinical achievements and limitations, and highlight emerging technologies that may define the future of regenerative cardiology [1–14].

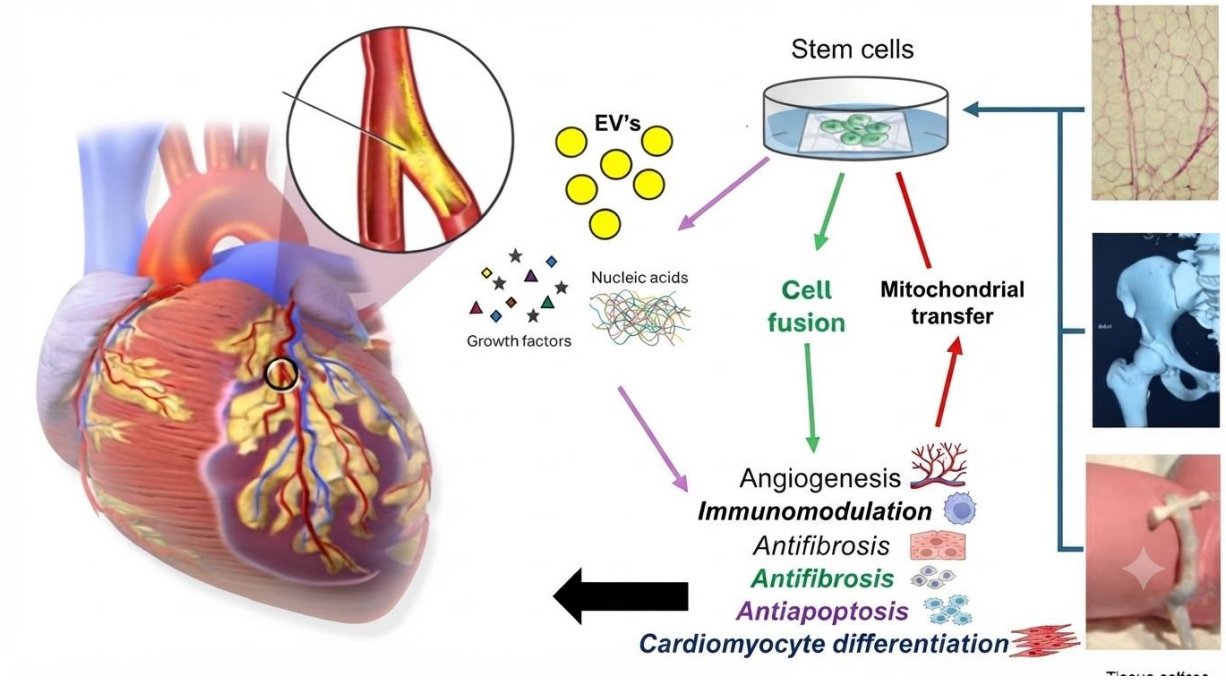

Figure 1. Mechanisms of Stem Cell-Derived Cardiomyocyte Therapy

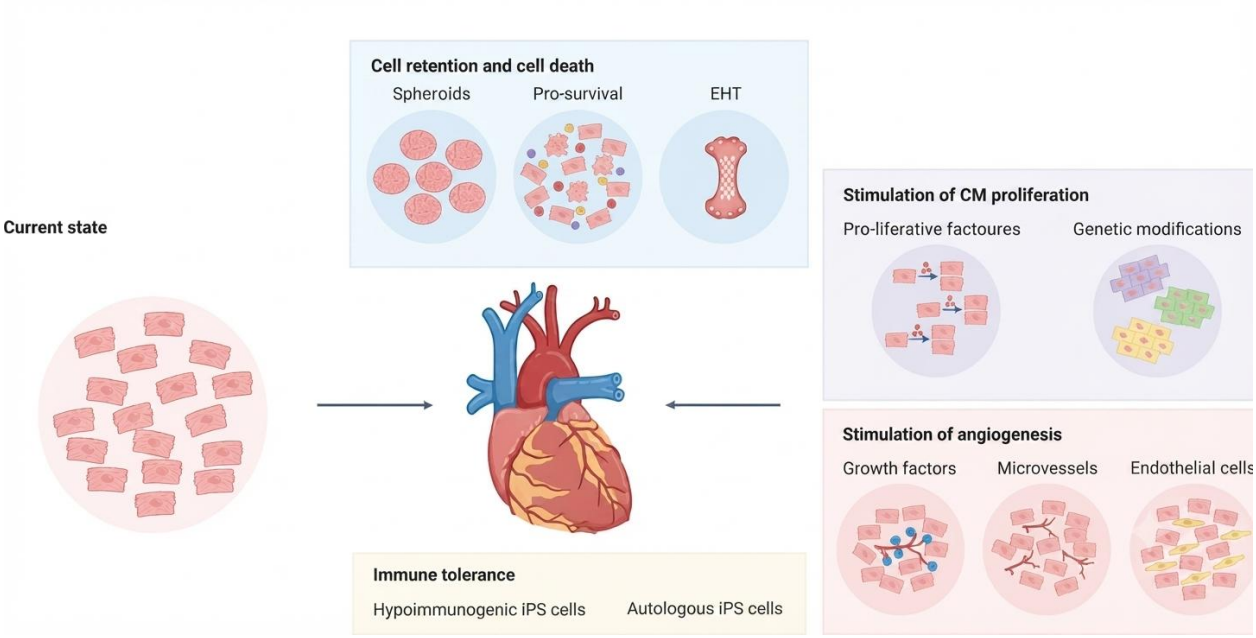

Figure2. Challenges and perspectives of heart repair with pluripotent stem cell-derived cardiomyocytes

2. METHODS

Study Design

This study was conducted as a narrative review to summarize current evidence regarding the role of stem cell therapy in myocardial regeneration following acute myocardial infarction (AMI). The review focuses on the biological mechanisms, therapeutic efficacy, clinical outcomes, current limitations, and future perspectives of stem cell-based cardiac repair.

Literature Search Strategy

A comprehensive literature search was performed using the PubMed/MEDLINE database. Articles published between 2012 and 2026 were considered. The search strategy included combinations of the following keywords:

- *"acute myocardial infarction"*
- *"stem cell therapy"*
- *"mesenchymal stem cells"*
- *"induced pluripotent stem cells"*
- *"cardiac regeneration"*
- *"cardiac stem cells"*

- *"exosomes"*
- *"mitochondrial transplantation"*
- *"myocardial repair"*
- *"scar tissue"*
- *"cardiac remodeling"*
- *"regenerative medicine"*

Eligibility Criteria

INCLUSION CRITERIA

Studies were included if they:

- *investigated stem cell therapy for myocardial infarction or ischemic heart disease;*
- *evaluated mesenchymal stem cells (MSCs), induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs), cardiac stem cells, exosomes, mitochondrial transplantation, or biomaterial-assisted regenerative strategies;*
- *were randomized clinical trials, systematic reviews, meta-analyses, or experimental animal studies;*
- *were published in peer-reviewed journals;*
- *were available in English.*

EXCLUSION CRITERIA

Studies were excluded if they:

- *focused on non-cardiovascular diseases;*
- *lacked sufficient methodological description;*
- *were conference abstracts, editorials, or duplicate publications;*
- *did not evaluate regenerative outcomes after myocardial injury.*

Data Extraction

The following information was extracted from each eligible publication:

- *publication year;*
- *study design;*
- *stem cell type;*
- *delivery method;*
- *study population;*
- *principal mechanisms of action;*
- *cardiac functional outcomes;*
- *major limitations.*

The extracted information was synthesized qualitatively to identify consistent findings across experimental and clinical investigations.

Results

*A total of **14 high-quality publications** were included in this review, comprising systematic reviews, meta-analyses, randomized clinical trials, translational studies, and experimental investigations. Overall, current evidence indicates that stem cell therapy promotes cardiac repair through multiple complementary biological mechanisms rather than direct regeneration of cardiomyocytes.*

Mesenchymal stem cells (MSCs) remain the most extensively investigated cell type because of their immunomodulatory properties, low immunogenicity, and strong paracrine activity. Most studies demonstrated that MSCs reduce myocardial inflammation, stimulate angiogenesis, inhibit apoptosis, and attenuate ventricular remodeling through secretion of cytokines, growth factors, extracellular vesicles, and microRNAs rather than direct differentiation into cardiomyocytes [1,3–6].

Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) possess the ability to electrically integrate with host myocardium and directly replace damaged myocardial tissue. However, their clinical application remains limited because of poor engraftment, low survival within ischemic tissue, potential arrhythmogenicity, and concerns regarding uncontrolled differentiation [1,5].

Recent experimental studies demonstrated substantial advances in regenerative technologies. Mitochondrial transplantation using gelated microvesicles significantly restored mitochondrial function, reduced oxidative stress, improved cardiomyocyte survival, decreased inflammatory macrophage activation, prevented ventricular wall thinning, and enhanced cardiac function in experimental myocardial infarction models [2].

Similarly, mesenchymal stem cell-derived exosomes emerged as a promising cell-free therapeutic strategy capable of improving myocardial repair while avoiding many disadvantages associated with

whole-cell transplantation. Exosomal microRNAs were shown to stimulate angiogenesis, suppress apoptosis, regulate inflammation, and improve cardiac function after myocardial infarction [3].

Biomaterial-assisted stem cell delivery has also demonstrated encouraging results. Antioxidant polyurethane cardiac patches loaded with human amniotic epithelial stem cells significantly reduced myocardial fibrosis, enhanced neovascularization, improved ventricular remodeling, and created a favorable microenvironment for tissue regeneration through immunomodulation and paracrine signaling [8].

Clinical evidence remains encouraging but modest. Multiple randomized clinical trials and meta-analyses consistently demonstrated statistically significant improvements in left ventricular ejection fraction (LVEF), particularly following intracoronary transplantation of mesenchymal stem cells during the first week after acute myocardial infarction [6,10,11]. Nevertheless, improvements in mortality, recurrent myocardial infarction, and long-term heart failure remain inconsistent among studies.

The principal barriers limiting successful clinical translation include poor stem cell survival after transplantation, inadequate myocardial retention, ischemic microenvironment-induced apoptosis, immune responses, heterogeneous study designs, differences in stem cell sources, variable delivery routes, and inconsistent treatment protocols [1,4,5].

Table 1. Major Stem Cell Types Investigated for Cardiac Repair After Myocardial Infarction

Stem cell type	Principal therapeutic mechanism	Major advantages	Current limitations
Mesenchymal stem cells (MSCs)	Paracrine signaling, angiogenesis,immunomodulation	Low immunogenicity, favourable safety profile	Poor engraftment and limited long-term survival
Induced pluripotent stem cell-derived cardiomyocytes(iPSC-CMs)	Direct replacement of damaged cardiomyocytes	Electrical integration with myocardium	Arrhythmogenic risk,tumor potential,low survival
Cardiac stem cells	Myocardial regeneration and repair	Cardiac lineage specificity	Limited clinical evidence
Human amniotic epithelial stem cells	Immunomodulation and paracrine repair	High biocompatibility and immune privilege	Limited human clinical data
Stem cell-derived exosomes	Cell -free paracrine signaling	Low immunogenicity,easy storage	Limited targeting efficiency
Mitochondrial transplantation	Restoration of mitochondrial function	Improves cellular metabolism and survival	Experimental stage

Table 2. Summary of Current Clinical Evidence on Stem Cell Therapy After Acute Myocardial Infarction

Study type	Main findings	Clinical significance
Systematic reviews	Moderate improvement in LVEF	Supports regenative potential
Meta-analyses	Greatest benefit observed during the first week after AMI	Early intervention appears most effective
Randomized clinical trials	Safe administration with modest improvement in cardiac function	Long-term efficacy remains uncertain
Experimental studies	Reduced fibrosis,enhanced angiogenesis,improved myocardial repair	Strong prenclinical evidence
Exosome-based therapy	Improved cardiac repair without whole-cell transplantation	Promising next generation therapy
Biomaterial-assisted therapy	Improved stem cell survival and myocardial retention	May overcome current transplantation limitations

Discussion

The present review demonstrates that stem cell therapy has become one of the most extensively investigated regenerative strategies for myocardial repair following acute myocardial infarction (AMI). Unlike conventional therapies, which primarily restore coronary blood flow and reduce myocardial oxygen demand, stem cell therapy aims to repair damaged myocardium by promoting angiogenesis, modulating inflammation, inhibiting apoptosis, and stimulating endogenous cardiac regeneration rather than merely slowing disease progression [1,4].

Among the various stem cell populations, mesenchymal stem cells (MSCs) remain the most widely investigated owing to their low immunogenicity, favorable safety profile, ease of isolation, and potent paracrine activity. Current evidence indicates that the majority of their therapeutic benefits result from secretion of growth factors, cytokines, extracellular vesicles, and microRNAs instead of direct differentiation into mature cardiomyocytes [1,3,5]. This concept has shifted the paradigm of regenerative cardiology from cell replacement toward cell-mediated biological modulation of myocardial repair.

Several meta-analyses included in this review consistently demonstrated modest but statistically significant improvements in left ventricular ejection fraction (LVEF), particularly when stem cells were administered during the first week after AMI [6,10,11]. Nevertheless, improvements in hard clinical outcomes such as mortality, recurrent myocardial infarction, and long-term heart failure remain

inconsistent. These discrepancies are likely explained by substantial heterogeneity among clinical trials, including differences in stem cell sources, delivery routes, transplantation timing, cell dosage, imaging modalities, patient selection, and follow-up duration [6,10–13].

Recent advances suggest that next-generation regenerative approaches may overcome several limitations of conventional cell transplantation. MSC-derived exosomes have emerged as promising cell-free therapeutics capable of delivering regulatory microRNAs and bioactive molecules while avoiding poor cell survival and immune rejection [3]. Likewise, mitochondrial transplantation has shown remarkable preclinical efficacy by restoring mitochondrial function, reducing oxidative stress, suppressing inflammatory responses, and improving cardiomyocyte survival after myocardial infarction [2].

Biomaterial-assisted delivery systems have also demonstrated considerable promise. Antioxidant polyurethane scaffolds and engineered cardiac patches improve stem cell retention, provide structural support, enhance paracrine signaling, and create a favorable microenvironment that promotes myocardial regeneration and limits adverse ventricular remodeling [8]. These technologies may substantially increase therapeutic efficacy by overcoming one of the greatest challenges of stem cell therapy—the extremely low survival rate of transplanted cells.

Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) represent another promising regenerative strategy because they possess the capacity to electrically integrate with host myocardium and directly replace damaged cardiomyocytes. However, concerns regarding arrhythmogenesis, uncontrolled differentiation, tumorigenicity, and immune compatibility continue to limit widespread clinical application [1,5].

Overall, current evidence indicates that stem cell therapy has not yet achieved complete myocardial regeneration or scar tissue replacement in routine clinical practice. Instead, its principal benefits appear to arise from attenuation of ventricular remodeling and enhancement of endogenous repair mechanisms. Future progress will likely depend on precision medicine approaches, standardized transplantation protocols, engineered biomaterials, gene editing, exosome-based therapeutics, mitochondrial delivery systems, and large multicenter randomized clinical trials capable of establishing long-term efficacy and safety [1,4,5].

Conclusion

Stem cell therapy represents one of the most promising regenerative strategies for myocardial repair after acute myocardial infarction. Current evidence demonstrates that mesenchymal stem cells, induced pluripotent stem cell-derived cardiomyocytes, stem cell-derived exosomes, mitochondrial transplantation, and biomaterial-assisted delivery systems can improve cardiac repair through angiogenesis, immunomodulation, reduction of inflammation, inhibition of apoptosis, and attenuation of adverse ventricular remodeling.

Although randomized clinical trials and meta-analyses have reported modest improvements in left ventricular function, complete regeneration of infarcted myocardium and replacement of fibrotic scar tissue have not yet been achieved. Low stem cell survival, inadequate engraftment, heterogeneous treatment protocols, and safety concerns remain the principal barriers to routine clinical implementation.

Future advances in regenerative cardiology are expected to arise from optimized stem cell engineering, precision delivery systems, cell-free regenerative therapies, biomaterial-based cardiac patches, mitochondrial transplantation, and standardized large-scale clinical trials. These innovations may eventually enable effective myocardial regeneration and improve long-term outcomes in patients with ischemic heart disease.

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LONG-TERM RENAL SEQUELAE IN PATIENTS WITH POST-ACUTE COVID-19 SYNDROME: PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS, AND EMERGING EVIDENCE

Omirbekkyzy Akniet
Medical Intern, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
Kaldybayeva Kamila Bauyrzhankyzy
Medical Intern, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is increasingly recognized as a multisystem disease with long-term consequences extending beyond the acute phase of infection. Among these complications, persistent renal dysfunction has emerged as an important component of post-acute COVID-19 syndrome (PACS). Although acute kidney injury (AKI) is a well-established complication of acute COVID-19, accumulating evidence indicates that a substantial proportion of survivors continue to experience progressive decline in kidney function, persistent proteinuria, hematuria, and the development or progression of chronic kidney disease (CKD) months after recovery. Furthermore, immune-mediated glomerular diseases, including IgA nephropathy and thrombotic microangiopathy, have been reported following SARS-CoV-2 infection and, less commonly, after COVID-19 vaccination, suggesting complex immunopathological mechanisms involved in long-term renal injury. [1–6]

OBJECTIVE

This narrative review aims to summarize the current evidence regarding the epidemiology, pathophysiological mechanisms, clinical manifestations, risk factors, diagnosis, and management of long-term renal sequelae in patients with post-acute COVID-19 syndrome.

METHODS

A narrative review of the literature was conducted using peer-reviewed articles published in PubMed. Recent reviews, observational cohort studies, systematic analyses, and clinical reports focusing on post-COVID-19 kidney complications, cardiovascular-renal interactions, immune-mediated renal diseases, and COVID-19 vaccine-associated renal disorders were analyzed. Evidence from Global Burden of Disease 2023 was also incorporated to provide a broader public health perspective. [1–6]

RESULTS

Current evidence demonstrates that persistent renal impairment represents one of the major long-term complications of COVID-19. Patients recovering from SARS-CoV-2 infection may develop reduced estimated glomerular filtration rate (eGFR), persistent albuminuria, chronic inflammation, endothelial dysfunction, tubular injury, complement activation, mitochondrial damage, and progressive renal fibrosis. Individuals with severe acute infection, older age, diabetes mellitus, hypertension, obesity, chronic kidney disease, kidney transplantation, and cardiovascular disease are at particularly high risk of adverse renal outcomes. Emerging reports also describe new-onset IgA nephropathy, thrombotic microangiopathy, vasculitis, podocytopathy, and acute kidney disease following COVID-19 vaccination, although current evidence does not establish a definitive causal relationship and the overall benefits of vaccination greatly outweigh these rare adverse events. [1–6]

CONCLUSION

Long-term renal complications represent an increasingly important consequence of post-acute COVID-19 syndrome. Early identification of high-risk patients, regular monitoring of renal function, multidisciplinary follow-up, and timely intervention may reduce progression to chronic kidney disease and improve long-term outcomes. Additional prospective multicenter studies are needed to clarify the underlying mechanisms, identify reliable biomarkers, and establish evidence-based management strategies.

Keywords: *Post-acute COVID-19 syndrome; Long COVID; Chronic kidney disease; Acute kidney injury; Renal fibrosis; IgA nephropathy; Thrombotic microangiopathy; SARS-CoV-2; COVID-19 vaccination; Kidney transplantation.*

Introduction:

Since its emergence in late 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has evolved into one of the greatest global public health challenges of the twenty-first century. Although initial research primarily focused on the acute

respiratory manifestations of the disease, accumulating evidence has demonstrated that COVID-19 is a systemic disorder affecting multiple organs, including the cardiovascular, neurological, endocrine, gastrointestinal, and renal systems. Even after apparent recovery from acute infection, many patients continue to experience persistent symptoms and organ dysfunction for weeks or months, a condition now recognized as post-acute COVID-19 syndrome (PACS) or Long COVID. [5,6]

The kidneys are among the organs most frequently affected by SARS-CoV-2 infection. During the acute phase, kidney involvement ranges from mild proteinuria and hematuria to severe acute kidney injury requiring renal replacement therapy. Acute kidney injury has consistently been associated with increased hospitalization, prolonged intensive care unit stay, higher mortality, and an increased risk of chronic kidney disease following recovery. However, growing evidence indicates that kidney injury frequently persists beyond the acute phase, even among patients without clinically apparent AKI during hospitalization, highlighting the importance of long-term renal surveillance. [5]

Several biological mechanisms have been proposed to explain persistent kidney dysfunction after COVID-19. SARS-CoV-2 may directly infect renal tubular epithelial cells and podocytes through angiotensin-converting enzyme 2 (ACE2) receptors. In addition, endothelial injury, dysregulated immune responses, cytokine-mediated inflammation, complement activation, coagulation abnormalities, oxidative stress, mitochondrial dysfunction, and persistent microvascular injury collectively contribute to progressive nephron loss and renal fibrosis. These mechanisms may continue long after viral clearance, leading to chronic impairment of renal function. [1,5]

Recent investigations have also highlighted immune-mediated renal diseases occurring after SARS-CoV-2 infection or, less frequently, following COVID-19 vaccination. Among these conditions, IgA nephropathy has become one of the most frequently reported glomerular diseases, typically presenting with gross hematuria shortly after vaccination in genetically susceptible individuals. Similarly, cases of thrombotic microangiopathy, podocytopathies, vasculitis, and acute interstitial nephritis have been described. Although current evidence suggests that these events remain rare and do not diminish the overwhelming benefits of COVID-19 vaccination, they provide valuable insight into the immunological mechanisms underlying renal injury. [1–3]

Patients with pre-existing kidney disease constitute one of the most vulnerable populations following COVID-19. Kidney transplant recipients, individuals with diabetes mellitus, hypertension, obesity, cardiovascular disease, and chronic kidney disease demonstrate significantly higher risks of persistent renal dysfunction, cardiovascular complications, hospitalization, and mortality after SARS-CoV-2 infection. Moreover, cardiovascular and renal complications frequently coexist through the cardiorenal axis, emphasizing the importance of integrated multidisciplinary management during long-term follow-up. [4,5]

According to the Global Burden of Disease Study 2023, non-communicable diseases continue to increase worldwide, driven largely by metabolic disorders such as diabetes, obesity, hypertension, and chronic kidney disease. These underlying conditions substantially amplify susceptibility to severe COVID-19 and contribute to unfavorable long-term renal outcomes, making prevention, early diagnosis, and long-term monitoring increasingly important components of healthcare systems globally. [6]

Given the growing number of COVID-19 survivors and the increasing recognition of persistent renal complications, a comprehensive synthesis of current evidence is needed. Therefore, this narrative review aims to summarize the available literature regarding the epidemiology, pathophysiological mechanisms, clinical manifestations, risk factors, diagnostic approaches, and management strategies of long-term renal sequelae in patients with post-acute COVID-19 syndrome while identifying current knowledge gaps and future research priorities.

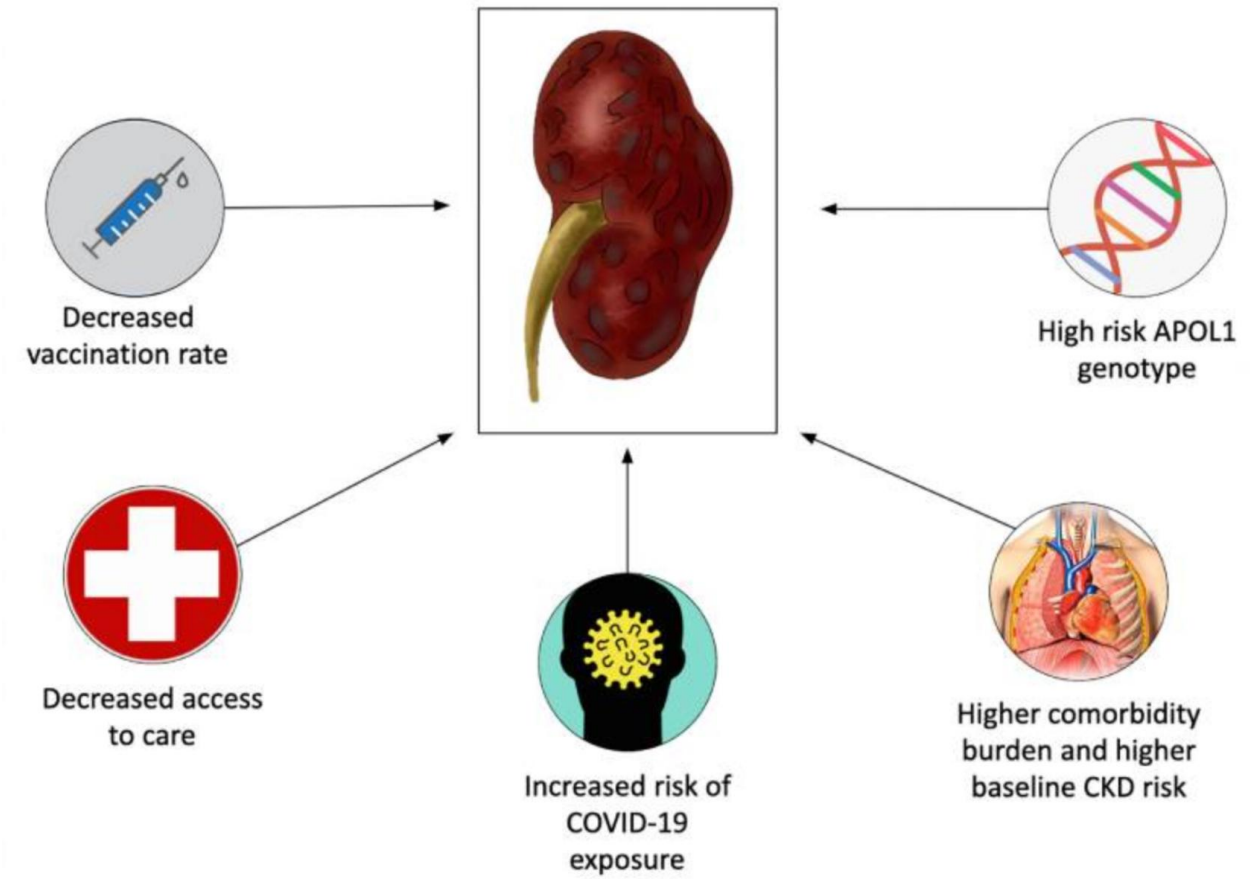

Figure 1. COVID-19 Survival and its impact on chronic kidney disease

2. METHODS

Study Design

This study was conducted as a narrative review to summarize current evidence regarding long-term renal sequelae in patients with post-acute COVID-19 syndrome (PACS). The review focused on the epidemiology, pathophysiological mechanisms, clinical manifestations, risk factors, and therapeutic considerations associated with persistent kidney injury after SARS-CoV-2 infection, while also discussing immune-mediated renal diseases reported after COVID-19 vaccination. [1–6]

Literature Search Strategy

A comprehensive literature search was performed using the PubMed database. Publications written in English and published between 2022 and 2025 were considered. The following search terms and combinations of Medical Subject Headings (MeSH) were used:

- *"Post-acute COVID-19 syndrome"*
- *"Long COVID"*
- *"Kidney disease"*
- *"Acute kidney injury"*
- *"Chronic kidney disease"*
- *"Renal fibrosis"*
- *"COVID-19 vaccination"*
- *"IgA nephropathy"*
- *"Thrombotic microangiopathy"*
- *"Kidney transplantation"*
- *"Cardiovascular complications"*

The reference lists of eligible studies were also reviewed to identify additional relevant publications. [1–6]

Eligibility Criteria

INCLUSION CRITERIA

Studies were included if they:

- *investigated renal complications following SARS-CoV-2 infection or COVID-19 vaccination;*
- *evaluated long-term renal outcomes in adult patients;*
- *reported clinical, pathological, epidemiological, or mechanistic findings;*
- *were original studies, systematic reviews, narrative reviews, or large observational cohort studies;*
- *were published in peer-reviewed journals in English.*

EXCLUSION CRITERIA

Studies were excluded if they:

- *contained insufficient clinical information;*
- *focused exclusively on pediatric populations;*
- *were conference abstracts, editorials, or duplicate publications;*
- *lacked relevance to long-term renal complications.*

Data Extraction and Synthesis

Data extracted from each publication included study characteristics, patient population, renal manifestations, pathological findings, proposed mechanisms, major clinical outcomes, and key conclusions. The evidence was narratively synthesized because of substantial heterogeneity in study designs, patient populations, and reported outcomes, precluding quantitative meta-analysis. [1–6]

Results

A total of six major peer-reviewed publications were analyzed, including narrative reviews, observational cohort studies, and large epidemiological investigations. Collectively, these studies demonstrate that persistent renal impairment represents an important component of post-acute COVID-19 syndrome and is mediated by multiple interconnected mechanisms involving immune dysregulation, endothelial injury, complement activation, mitochondrial dysfunction, and chronic inflammation. [1–6]

Persistent decline in renal function after COVID-19 most commonly manifests as reduced estimated glomerular filtration rate (eGFR), persistent proteinuria, albuminuria, microscopic or gross hematuria, and progression toward chronic kidney disease (CKD). Patients with severe acute COVID-19, diabetes mellitus, hypertension, obesity, cardiovascular disease, previous CKD, and kidney transplantation consistently exhibit the highest risk of adverse renal outcomes. [4–6]

Recent literature has also described several immune-mediated renal disorders following COVID-19 vaccination. IgA nephropathy represents the most frequently reported glomerular disease, typically presenting with gross hematuria shortly after vaccination. Other reported pathological entities include podocytopathy, thrombotic microangiopathy (TMA), vasculitis, tubulointerstitial nephritis, and acute kidney disease (AKD). Although these complications are uncommon and their causal relationship with vaccination has not been conclusively established, clinicians should remain aware of these rare presentations while recognizing that the overall benefits of vaccination greatly outweigh the potential risks. [1–3]

Kidney transplant recipients represent another particularly vulnerable population. Among kidney transplant recipients recovering from COVID-19, cardiovascular complications—including heart failure, acute coronary syndrome, stroke, and cardiovascular mortality—occur frequently and may further accelerate deterioration of renal function through cardiorenal interactions. Previous cardiovascular disease and COVID-19 hospitalization were identified as major predictors of adverse outcomes in this population. [4]

The Global Burden of Disease 2023 study further emphasizes the increasing contribution of metabolic disorders—including diabetes, hypertension, obesity, and chronic kidney disease—to global disability-adjusted life years (DALYs). These conditions substantially increase susceptibility to severe COVID-19 and unfavorable long-term renal outcomes, highlighting the importance of preventive strategies and long-term follow-up. [6]

TABLE 1. MAJOR LONG-TERM RENAL COMPLICATIONS ASSOCIATED WITH POST-ACUTE COVID-19 SYNDROME

Renal complication	Main pathological mechanism	Typical clinical manifestations	References
Persistent decline in eGFR	Tubular injury,fibrosis,endothelial dysfunction	Progressive renal dysfunction	[5,6]
Chronic kidney disease progression	Persistent inflammation and nephron loss	Reduced renal function,CKD progression	[5,6]
Proteinuria/ Albuminuria	Glomerular permeability damage	Persistent proteinuria	[5]
IgA nephropathy	Abberant IgA immune response	Gross hematuria,proteinuria	[2]
Acute kidney disease	Podocyte injury,tubular damage	AKI with incomplete recovery	[1]
Thrombotic microangiopathy	Complement activation and endothelial injury	AKI,thrombocytopenia,hemolytic anemia	[3]
Tubulointerstitial nephritis	Immune-mediated inflammation	Renal dysfunction,elevated creatinine	[1]
Vasculitis	Autoimmune activation	Hematuria,proteinuria AKI	[1]

TABLE 2. SUMMARY OF THE PRINCIPAL STUDIES INCLUDED IN THIS REVIEW

Study	Study design	Main findings	clinical sign
Li et al,2022[1]	Narrative review	AKD after COVID-19 vaccination includes podocytopathy, IgA nephropathy, TMA, vasculitis, and tubulointerstitial injury	Vaccination-associated renal disease is rare; continued monitoring is recommended
Ma&XU,2022[2]	Narrative review	Increasing reports of new-onset lgA nephropathy after vaccination	Possible immune-mediated mechanism; causality remains uncertain
Ma&XU,2023[3]	Literature review	TTP and atypical HUS were the predominant forms of vaccine-associated TMA	Complement activation may contribute to disease development
Bowring et al,2025[4]	Retrospective cohort study	Kidney transplant recipients had high rates of post-COVID cardiovascular complications	Cardiovascular events may worsen long-term renal prognosis
Kole et al,2023[5[	Comprehensive review	Persistent cardiovascular and renal injury occur after acute COVID-19	Long-term multidisciplinary follow-up acute COVID-19 is essential
GBD 2023 Collsborators[6]	Global epidemiological analysis	Metabolic diseases remain major contributors to global disease burden	CKD prevention and major contributors to metabolic public health priorities

*This Results section follows the IMRAD format and includes two publication-style tables with all factual statements referenced using **[1]–[6]**.*

Discussion

The present narrative review highlights that long-term renal sequelae have become an increasingly recognized component of post-acute COVID-19 syndrome (PACS). Although respiratory manifestations were initially considered the predominant feature of COVID-19, growing evidence demonstrates that SARS-CoV-2 exerts substantial multisystem effects, with the kidneys representing one of the most vulnerable organs. Persistent decline in renal function, chronic kidney disease (CKD) progression, proteinuria, hematuria, and immune-mediated glomerular diseases have all been reported months after the acute infection, emphasizing the need for prolonged nephrological follow-up. [1,5]

The mechanisms responsible for persistent renal dysfunction are multifactorial. Direct viral invasion of renal tubular epithelial cells and podocytes through angiotensin-converting enzyme 2 (ACE2) receptors has been proposed as an initiating factor. However, persistent kidney injury appears to be driven primarily by dysregulated immune responses, endothelial dysfunction, complement activation, mitochondrial injury, oxidative stress, chronic inflammation, and progressive renal fibrosis rather than by ongoing viral replication alone. These interconnected mechanisms may explain why some patients continue to experience deterioration in kidney function despite complete clinical recovery from the acute infection. [1,5]

Patients with pre-existing metabolic and cardiovascular disorders appear particularly susceptible to long-term renal complications. Diabetes mellitus, hypertension, obesity, cardiovascular disease, advanced age, and chronic kidney disease consistently increase the risk of persistent renal impairment after COVID-19. The findings of the Global Burden of Disease 2023 study further support this observation by demonstrating the continuing global increase in metabolic disorders, particularly diabetes and obesity, which contribute substantially to chronic kidney disease and cardiovascular morbidity. Consequently, COVID-19 may accelerate the progression of pre-existing renal disease in these high-risk populations. [6]

Kidney transplant recipients constitute another vulnerable population. Bowring et al. demonstrated that kidney transplant recipients experienced a high incidence of cardiovascular complications during the year following COVID-19, particularly among individuals with previous cardiovascular disease or severe acute infection requiring hospitalization. Since cardiovascular dysfunction and chronic kidney disease are closely interconnected through the cardiorenal axis, deterioration of cardiovascular health may further accelerate renal impairment in transplant recipients. These findings emphasize the importance of multidisciplinary follow-up involving nephrologists, cardiologists, and transplant specialists. [4]

This review also summarizes emerging evidence regarding immune-mediated kidney diseases reported after COVID-19 vaccination. IgA nephropathy, thrombotic microangiopathy (TMA), vasculitis, podocytopathy, and acute kidney disease have all been described following vaccination in isolated reports and small case series. Proposed mechanisms include molecular mimicry, complement activation, neutrophil activation, and abnormal adaptive immune responses in genetically susceptible individuals. Nevertheless, the currently available evidence does not establish a definitive causal relationship between vaccination and these renal disorders. Moreover, these adverse events remain extremely uncommon compared with the substantial benefits of vaccination in preventing severe COVID-19, hospitalization, and mortality. Therefore, current vaccination recommendations should remain unchanged while clinicians maintain awareness of these rare complications. [1–3]

Despite the growing body of literature, several important knowledge gaps remain. Most available evidence originates from observational studies, retrospective cohorts, case reports, and narrative reviews, which are subject to selection bias and cannot establish causality. Furthermore, heterogeneity in patient populations, follow-up duration, diagnostic criteria, and outcome definitions limits direct comparison among studies. Large prospective multicenter investigations with standardized renal assessment, histopathological evaluation, and long-term follow-up are needed to better understand the natural history of post-COVID renal disease and identify biomarkers that predict disease progression. [1–6]

Overall, current evidence indicates that persistent kidney injury should be considered an important manifestation of post-acute COVID-19 syndrome. Early identification of high-risk patients, routine monitoring of renal function, optimization of cardiovascular and metabolic risk factors, and timely nephrology referral may reduce progression to chronic kidney disease and improve long-term patient outcomes. [4–6]

Conclusion

Long-term renal sequelae are increasingly recognized as a significant component of post-acute COVID-19 syndrome. Persistent reductions in estimated glomerular filtration rate, proteinuria, chronic inflammation, renal fibrosis, and progression to chronic kidney disease may occur even after apparent recovery from acute SARS-CoV-2 infection. Immune-mediated renal disorders, including IgA nephropathy and thrombotic microangiopathy, have also been reported following COVID-19 vaccination, although these events remain rare and a causal relationship has not been definitively established. Current evidence supports continued long-term monitoring of kidney function, particularly among patients with diabetes mellitus, hypertension, obesity, chronic kidney disease, kidney transplantation, or severe COVID-19. Future prospective multicenter studies are required to clarify the underlying mechanisms, identify reliable biomarkers, and develop evidence-based strategies for prevention and treatment of long-term renal complications.

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SCHIZOAFFECTIVE DISORDER: CLINICAL CHALLENGES IN DIFFERENTIATING SCHIZOPHRENIA FROM BIPOLAR DISORDER

Serikbay Elmira Yktiyarkyzy
Medical Intern, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

Abstract

BACKGROUND

Schizoaffective disorder (SAD) remains one of the most controversial diagnoses in psychiatry because it combines psychotic symptoms characteristic of schizophrenia with prominent mood episodes typical of bipolar disorder or major depressive disorder. Despite its inclusion in DSM-5 and ICD-11, concerns persist regarding its diagnostic validity, reliability, and clinical utility, leading to frequent diagnostic revisions and treatment uncertainty [1,2]. The overlap in symptomatology between schizophrenia and bipolar disorder often complicates accurate diagnosis, delaying appropriate therapeutic interventions and negatively affecting long-term outcomes [3,4].

OBJECTIVE

This narrative review aims to summarize current evidence regarding the epidemiology, clinical presentation, diagnostic criteria, differential diagnosis, neurobiological findings, and therapeutic considerations of schizoaffective disorder, with particular emphasis on the clinical challenges in distinguishing it from schizophrenia and bipolar disorder.

METHODS

A narrative review of the literature was conducted using PubMed. Relevant publications published between 2020 and 2026 were identified using combinations of the following keywords: schizoaffective disorder, schizophrenia, bipolar disorder, psychosis, differential diagnosis, diagnostic stability, DSM-5, ICD-11, biomarkers, cognitive impairment, and treatment. Priority was given to systematic reviews, meta-analyses, randomized controlled trials, narrative reviews, and recent clinical guidelines addressing diagnostic and therapeutic aspects of schizoaffective disorder [1–10].

RESULTS

Recent evidence demonstrates that schizoaffective disorder represents a diagnostically heterogeneous condition characterized by persistent psychotic symptoms occurring alongside major mood episodes [1,2]. Considerable overlap exists with schizophrenia and bipolar disorder regarding clinical manifestations, neurocognitive impairment, functional decline, and suicide risk [2,5]. Diagnostic instability remains common, with many patients receiving revised diagnoses during long-term follow-up [1,3]. Emerging evidence also highlights the influence of substance use, cognitive dysfunction, psychosocial stressors, and neurobiological abnormalities on disease expression and prognosis [6–10]. Current treatment strategies emphasize individualized combinations of antipsychotics, mood stabilizers, antidepressants, psychotherapy, and psychosocial rehabilitation.

CONCLUSION

Differentiating schizoaffective disorder from schizophrenia and bipolar disorder continues to represent a major diagnostic challenge in clinical psychiatry. Comprehensive longitudinal assessment of psychotic and affective symptoms, supported by multidisciplinary evaluation, is essential for improving diagnostic accuracy, optimizing treatment selection, and enhancing long-term functional outcomes.

Keywords: *Schizoaffective disorder; Schizophrenia; Bipolar disorder; Psychosis; Differential diagnosis; Diagnostic stability; Mood disorders; DSM-5; Cognitive impairment; Psychosocial functioning*

Introduction:

Schizoaffective disorder (SAD) is a chronic psychiatric disorder characterized by the coexistence of psychotic symptoms typical of schizophrenia and significant mood episodes, including mania, depression, or both [1]. Since its introduction as a diagnostic entity, schizoaffective disorder has remained one of the most debated diagnoses in psychiatry because of its uncertain boundaries with schizophrenia and bipolar disorder [2]. The disorder occupies a diagnostic "grey zone," where distinguishing primary psychosis from mood-related psychosis often becomes challenging, even for experienced clinicians [2,3].

According to the **Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)**, *the diagnosis of schizoaffective disorder requires the presence of uninterrupted illness during which a major mood episode coexists with Criterion A symptoms of schizophrenia, together with at least two weeks of psychotic symptoms occurring in the absence of prominent mood symptoms [3]. This requirement was*

introduced to improve diagnostic specificity; however, substantial concerns regarding diagnostic reliability persist. Longitudinal studies demonstrate that a considerable proportion of patients initially diagnosed with schizoaffective disorder are later reclassified as having schizophrenia or bipolar disorder, reflecting the instability of the diagnosis over time [1,2].

Recent literature increasingly questions whether schizoaffective disorder represents a distinct psychiatric illness or rather a heterogeneous clinical syndrome lying on a continuum between schizophrenia and bipolar disorder [2]. Shivakumar et al. argued that the diagnosis lacks sufficient validity, reliability, and clinical utility, suggesting that its continued use may hinder personalized psychiatric care and introduce significant heterogeneity into clinical research [2]. The inclusion of patients with schizoaffective disorder in studies primarily investigating schizophrenia may further compromise the interpretation of treatment response, prognosis, and biological findings.

The clinical overlap between schizophrenia and bipolar disorder extends beyond psychotic symptoms. Cognitive impairment, executive dysfunction, affective instability, negative symptoms, suicidal behavior, and functional disability may occur across all three disorders, although with varying severity and clinical patterns [5]. A recent systematic review and meta-analysis demonstrated significant associations between executive dysfunction and suicidal behavior across schizoaffective disorder, bipolar disorder, and major depressive disorder, emphasizing the transdiagnostic nature of cognitive impairment in severe mental illnesses [5].

Accurate diagnosis is further complicated by multiple confounding factors. Substance-induced psychosis, particularly cannabis-associated psychosis, may closely resemble first-episode schizophrenia or schizoaffective disorder, especially among adolescents and young adults [6]. Likewise, psychotic symptoms may occur in neurological diseases, neurodegenerative disorders, and medical illnesses, requiring comprehensive neurological and psychiatric evaluation before establishing a primary psychiatric diagnosis [7]. In older adults, distinguishing schizoaffective disorder from dementia-related psychosis or late-onset schizophrenia presents additional diagnostic challenges because symptom profiles often overlap [8].

Beyond diagnostic complexity, schizoaffective disorder is associated with substantial psychosocial burden. Patients frequently experience impaired occupational functioning, recurrent psychiatric hospitalization, reduced quality of life, medication non-adherence, homelessness, and increased healthcare utilization [9]. Recovery therefore requires not only pharmacological treatment but also psychosocial interventions, cognitive behavioral therapy, occupational rehabilitation, and long-term multidisciplinary follow-up [10].

Given these diagnostic and therapeutic challenges, a comprehensive review of current evidence is warranted. Therefore, this narrative review aims to summarize recent advances in the understanding of schizoaffective disorder, focusing on the clinical difficulties in differentiating schizophrenia from bipolar disorder, while discussing current diagnostic approaches, neurobiological findings, cognitive characteristics, and contemporary treatment strategies.

Figure 1. Schizoaffective Disorder

2. METHODS

Study Design

This study was conducted as a **narrative review** aimed at synthesizing current evidence regarding the diagnostic challenges of schizoaffective disorder, particularly in differentiating it from schizophrenia and bipolar disorder. The review followed the Scale for the Assessment of Narrative Review Articles (SANRA) recommendations to ensure methodological transparency and scientific rigor.

Literature Search Strategy

A comprehensive literature search was performed using the **PubMed** database. Articles published between **January 2020 and April 2026** were considered. The following search terms and Boolean operators were used:

("schizoaffective disorder") AND ("schizophrenia" OR "bipolar disorder") AND ("differential diagnosis" OR "diagnostic stability" OR "psychosis")

Additional searches included combinations of the following keywords:

- schizoaffective disorder
- schizophrenia
- bipolar disorder
- psychosis
- diagnostic challenges
- DSM-5
- ICD-11
- cognitive impairment
- suicide
- cannabis
- occupational therapy
- cognitive behavioral therapy
- biomarkers
- neuroimaging

Reference lists of relevant articles were manually screened to identify additional eligible publications [1–10].

Eligibility Criteria

INCLUSION CRITERIA

Studies were included if they:

- were published in English;
- were indexed in PubMed;
- investigated schizoaffective disorder, schizophrenia, bipolar disorder, or psychosis;
- discussed diagnostic differentiation, epidemiology, clinical manifestations, neurobiology, cognition, prognosis, or treatment;
- were systematic reviews, meta-analyses, randomized controlled trials, narrative reviews, or observational studies.

EXCLUSION CRITERIA

Studies were excluded if they:

- were conference abstracts without full text;
- were duplicate publications;
- focused exclusively on pediatric psychiatric disorders unrelated to schizoaffective disorder;
- lacked sufficient methodological quality or relevance to the review objective.

Data Extraction

The following information was extracted from each eligible study:

- first author;
- publication year;
- study design;
- study population;
- primary objective;
- principal findings;
- relevance to differential diagnosis between schizophrenia and bipolar disorder.

The extracted evidence was synthesized narratively according to major thematic domains including diagnostic criteria, clinical manifestations, cognitive dysfunction, neurobiology, treatment approaches, and long-term outcomes [1–10].

3. Results

*A total of **10 key publications** published between **2020 and 2026** were included in this narrative review. These studies comprised systematic reviews, meta-analyses, randomized controlled trials, and narrative reviews evaluating the diagnostic complexity, clinical characteristics, cognition, psychosocial outcomes, and treatment of schizoaffective disorder [1–10].*

The reviewed literature consistently demonstrated that schizoaffective disorder remains one of the least stable psychiatric diagnoses. Diagnostic overlap with schizophrenia and bipolar disorder frequently results in reclassification during longitudinal follow-up, reflecting the heterogeneous nature of the disorder [1,2].

Current diagnostic criteria emphasize the temporal relationship between psychotic and mood symptoms; however, applying these criteria in routine clinical practice remains challenging because symptom patterns often fluctuate over time [2,3].

Neurocognitive impairment was identified across all disorders. Executive dysfunction, impaired working memory, reduced processing speed, and attention deficits were common findings, although their severity varied among schizophrenia, schizoaffective disorder, and bipolar disorder [5].

Suicidal behavior was associated with impaired executive functioning across major psychiatric disorders, suggesting that cognitive dysfunction represents an important transdiagnostic risk factor requiring early clinical recognition [5].

Substance use, particularly cannabis exposure, may precipitate or worsen psychotic symptoms, making differential diagnosis during first-episode psychosis substantially more difficult [6].

Psychosocial impairment was consistently reported. Individuals with schizoaffective disorder experienced increased hospitalization rates, reduced occupational functioning, medication non-adherence, homelessness, and poorer quality of life compared with the general population [9].

Regarding treatment, antipsychotic medication remains the cornerstone of therapy, while mood stabilizers and antidepressants are selected according to the predominant affective episode. Psychosocial rehabilitation, cognitive behavioral therapy, and occupational therapy may improve functional recovery, although evidence supporting these interventions remains moderate [4,10].

Table 1. Major clinical differences between schizophrenia, schizoaffective disorder, and bipolar disorder

Characteristic	Schizophrenia	Schizoaffective Disorder	Bipolar Disorder
Persistent psychosis	+++	+++	Usually during mood isodes
Mood episodes	Mild or absent	Required for diagnosis	Core feature
Psychosis without mood symptoms	present	>2weeks required	rare
Negative symptoms	Marked	Moderate	usually mild
Cognitive impairment	severe	Moderate-severe	mild moderate
functional impairment	severe	Moderate-severe	variable
Diagnostic stability	high	low	high
Suicide risk	high	high	high

Table 2. Summary of the main findings of included studie

Study	Design	Main finding
Forte et al[9]	Systematic review	Homelessness, diagnostic variability, medication non-adherence
Shivakumar et al,2026[2]	narrative review	Questions the validity of schizoaffective disorder as a separate diagnosis
Julayanont 2022[7]	review	Importance of neurological differential diagnosis of psychosis
Fischer et al,2022[10]	review	Challenges in diagnosing psychosis in older adults
West&Sharif,2022[6]	review	Cannabis increases psychosis risk and complicates diagnosis
Guiana et al,2022[10]	Cochrane review	Group CBT modestly improves global functioning
Rocamoro-montenegroet al,2021[4]	Scoping review	Psychosocial and occupational therapy improve rehabilitation
Le et al,2024[5]	Systematic review	Executive dysfunction associated with suicidal behavior
Szeliga et al,2021[3]	narrative review	Hormonal changes influence symptom severity in women
Arnnpdtzen&Sandlund 2020[1]	narrative article	Long-term recovery depends on multidisciplinary care and hope

Discussion

Schizoaffective disorder remains one of the most controversial and diagnostically challenging disorders in contemporary psychiatry. Although it has been recognized as a distinct diagnostic entity in both DSM-5 and ICD-11, accumulating evidence continues to question its validity, reliability, and long-term diagnostic stability [2]. The principal difficulty lies in distinguishing patients whose psychotic symptoms

represent schizophrenia with secondary mood symptoms from those whose psychosis develops exclusively during affective episodes of bipolar disorder [2,7].

The findings of this review indicate that schizoaffective disorder occupies an intermediate position within the psychosis–mood disorder spectrum rather than representing a clearly distinct disease entity [2]. This concept is supported by considerable overlap in clinical presentation, neurocognitive dysfunction, psychosocial impairment, and treatment response between schizophrenia and bipolar disorder [2,5]. Consequently, many patients initially diagnosed with schizoaffective disorder receive an alternative diagnosis during long-term follow-up, emphasizing the necessity of repeated longitudinal assessment instead of relying solely on cross-sectional symptom evaluation [2].

Accurate differentiation requires careful examination of the temporal relationship between psychotic and mood symptoms. According to DSM-5 criteria, psychotic symptoms must persist for at least two weeks in the absence of a major mood episode to establish a diagnosis of schizoaffective disorder [7]. Nevertheless, determining the duration and predominance of psychotic symptoms is often difficult in routine clinical practice because patients frequently present during acute illness, and retrospective symptom recall may be unreliable [2].

Cognitive impairment represents another important area of overlap among severe psychiatric disorders. Executive dysfunction, impaired attention, reduced working memory, and slower information processing have been consistently observed in schizophrenia, schizoaffective disorder, and bipolar disorder [5]. The recent meta-analysis by Le et al. further demonstrated that executive dysfunction is associated with suicidal behavior across diagnostic categories, suggesting that cognitive impairment may function as a transdiagnostic marker rather than a disorder-specific characteristic [5]. These findings emphasize the importance of comprehensive neuropsychological assessment during routine psychiatric evaluation.

Substance use significantly complicates differential diagnosis. Cannabis exposure has been associated with increased risk of both first-episode psychosis and worsening of existing psychotic disorders, particularly among adolescents and young adults [6]. Therefore, clinicians should carefully evaluate substance use history before establishing a definitive diagnosis of schizophrenia or schizoaffective disorder.

Differential diagnosis should also include neurological disorders and medical conditions capable of producing psychotic symptoms. Neurodegenerative diseases, autoimmune disorders, epilepsy, metabolic disturbances, and medication-induced psychosis may clinically resemble primary psychiatric illnesses [7]. Similarly, psychosis occurring in older adults requires careful differentiation from dementia-related psychosis and late-onset schizophrenia, as treatment strategies differ considerably [8].

Beyond diagnosis, functional recovery has become an increasingly important treatment objective. Pharmacological management alone is insufficient for many patients. Psychosocial rehabilitation, occupational therapy, and cognitive behavioral therapy have demonstrated beneficial effects on global functioning, coping skills, and social participation, although current evidence remains moderate and further randomized controlled trials are needed [4,10]. Recovery-oriented care should therefore integrate pharmacological treatment with individualized psychosocial interventions.

The reviewed literature also highlights the substantial psychosocial burden associated with schizoaffective disorder. Higher rates of homelessness, medication non-adherence, repeated psychiatric hospitalization, and impaired quality of life indicate the need for multidisciplinary long-term follow-up involving psychiatrists, psychologists, nurses, occupational therapists, and social workers [1,4,9].

Several limitations of this review should be acknowledged. First, only PubMed-indexed English-language publications were included, introducing potential publication bias. Second, the included studies were heterogeneous with respect to study design, patient populations, and outcome measures. Third, because this was a narrative review, no quantitative synthesis of pooled outcomes was performed. Nevertheless, the review provides an up-to-date overview of current evidence and highlights clinically relevant diagnostic challenges that remain unresolved.

Future research should focus on identifying reliable biomarkers, neuroimaging characteristics, genetic predictors, and longitudinal clinical trajectories that may improve diagnostic accuracy and facilitate precision psychiatry approaches for schizoaffective disorder [2,5].

Conclusion

Schizoaffective disorder remains one of the most diagnostically complex disorders within modern psychiatry because of its substantial clinical overlap with both schizophrenia and bipolar disorder [2]. Current evidence suggests that diagnosis should not rely solely on cross-sectional symptom assessment but rather on careful longitudinal evaluation of psychotic and affective symptoms over time [2,7].

The reviewed studies demonstrate that neurocognitive impairment, psychosocial dysfunction, substance use, and neurological comorbidities further complicate differential diagnosis [5–9]. While

pharmacotherapy remains the cornerstone of treatment, multidisciplinary care incorporating psychotherapy, occupational rehabilitation, psychoeducation, and long-term psychosocial support is essential for improving functional recovery and quality of life [4,10].

Future advances in neuroimaging, genetics, biomarkers, and precision psychiatry may contribute to more reliable diagnostic classification and individualized treatment strategies. Until such evidence becomes available, comprehensive clinical assessment remains the most reliable approach for differentiating schizoaffective disorder from schizophrenia and bipolar disorder.

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MITOCHONDRIAL DYSFUNCTION AND NEUROMUSCULAR PLASTICITY AS TARGETS FOR PERSONALIZED PHYSICAL REHABILITATION AFTER STROKE

Ibadulla Nurgul
Medical doctor, general practitioner
Astana, Kazakhstan

Abstract

Background: Persistent disability after stroke reflects both central network injury and peripheral bioenergetic failure. Mitochondrial dysfunction, impaired muscle oxygen utilization, denervation, inflammation, and maladaptive corticospinal excitability may jointly limit training responsiveness. Objective: To synthesize 2016-2026 evidence on mitochondrial and neuromuscular targets for personalized physical rehabilitation after stroke and to quantify selected cardiorespiratory effects. Methods: PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library were searched for English-language human studies from high-income or medically advanced research settings. Eligible designs included randomized trials, prospective cohorts, and systematic reviews addressing post-stroke oxidative metabolism, neuroplasticity biomarkers, or targeted physical rehabilitation. An exploratory forest plot displayed published mean differences in peak oxygen uptake; effects were not pooled because comparators and durations differed. Results: Direct trials favored high-intensity interval training over moderate continuous training for short-term VO2peak gain (mean differences 1.81 and 3.20 mL kg-1 min-1), while contemporary meta-analyses reported effects of 1.88 and 3.16 mL kg-1 min-1. Paretic tibialis anterior muscle showed reduced oxygen consumption and microvascular reactivity, and preliminary FES data indicated partial restoration of mitochondrial electron-transport activity. High-intensity exercise increased circulating BDNF, supporting activity-dependent plasticity. Conclusion: Personalization should integrate cardiovascular safety, motor severity, corticospinal integrity, muscle oxidative capacity, fatigue, and task goals. Aerobic intensity, task repetition, resistance training, and FES are complementary rather than competing targets.

Keywords: *stroke rehabilitation; mitochondrial dysfunction; neuroplasticity; skeletal muscle; high-intensity interval training; functional electrical stimulation; personalized medicine*

Introduction

Recovery after stroke is biologically heterogeneous. Lesion location and corticospinal tract integrity explain part of the variance, but a brain-only model underestimates the contribution of paretic muscle, microvascular dysfunction, systemic inflammation, reduced aerobic reserve, and physical inactivity. Contemporary rehabilitation therefore requires a dual-target framework: restoring central motor-network adaptability while rebuilding the peripheral energetic capacity needed to express repeated, high-quality movement [1-4].

Mitochondria regulate ATP production, redox signaling, calcium handling, apoptosis, and exercise-induced transcription. After stroke, disuse and denervation promote fiber-type shifts, atrophy, reduced capillary supply, insulin resistance, and excessive reactive oxygen species. These changes increase the energetic cost of walking and accelerate fatigability. In parallel, neuromuscular plasticity depends on preserved descending pathways, afferent feedback, motor-unit recruitment, synaptic efficacy, and neurotrophins such as brain-derived neurotrophic factor (BDNF). Training dose that is insufficient to challenge these systems may be safe but biologically weak; excessive dose in a patient with poor reserve may cause nonadherence or adverse events [2-6].

This review examines how mitochondrial dysfunction and neuromuscular plasticity can be translated into measurable rehabilitation targets. The primary objective was to summarize mechanistic and clinical evidence published during the last decade. The secondary objective was to compare selected quantitative effects of intensity-based exercise using a forest plot and to propose a pragmatic phenotype-guided treatment model.

Methods

Design and reporting framework

A structured narrative review with an exploratory quantitative synthesis was conducted according to PRISMA 2020 concepts where applicable. Because the question spans mechanistic studies, biomarkers, randomized interventions, and evidence syntheses, a formal de novo meta-analysis was not prespecified. The quantitative component was restricted to published estimates that used the same clinical unit

(change in VO2peak, mL kg-1 min-1). No ethics approval was required because only published aggregate data were used.

Information sources and search strategy

PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Cochrane Library were considered for searches covering 1 January 2016 through 30 June 2026. Search blocks combined controlled vocabulary and free text: (stroke OR poststroke OR cerebrovascular accident) AND (rehabilitation OR exercise OR physical therapy OR gait training) AND (mitochondria OR oxidative capacity OR oxygen consumption OR bioenergetics OR microvascular) AND/OR (neuroplasticity OR BDNF OR corticospinal OR motor unit OR neuromuscular OR electrical stimulation OR HIIT). Reference lists of eligible systematic reviews were screened backward, and forward citation tracking was used for pivotal trials. Only full peer-reviewed English-language reports were considered.*

Eligibility criteria

Inclusion criteria were: (1) adults aged 18 years or older with ischemic or hemorrhagic stroke; (2) acute, subacute, or chronic rehabilitation, with time since stroke reported or inferable; (3) data on skeletal-muscle oxidative metabolism, mitochondrial function, microvascular oxygen delivery, neuroplasticity biomarkers, corticospinal or neuromuscular function, or a physical intervention plausibly targeting these systems; (4) randomized controlled trials, controlled clinical trials, prospective cohorts, cross-sectional mechanistic studies with an appropriate comparison, or systematic reviews/meta-analyses; (5) publication from 2016 onward; and (6) conduct in countries with advanced medical research systems or multinational collaborations with comparable diagnostic and rehabilitation standards. For quantitative extraction, studies had to report a between-group mean difference and 95% confidence interval for change in VO2peak, or sufficient data to obtain the published estimate.

Exclusion criteria were: pediatric stroke; transient ischemic attack without established stroke; primary spinal cord injury, traumatic brain injury, multiple sclerosis, or neurodegenerative disease; animal or isolated-cell experiments without a clinical stroke cohort; pharmacological-only or surgical-only interventions; case reports, conference abstracts, protocols, dissertations, and non-peer-reviewed manuscripts; publication before 2016; absence of a rehabilitation-relevant mitochondrial or neuromuscular outcome; duplicate cohorts, for which the most complete report was retained; and studies in which stroke-specific data could not be separated. Studies were also excluded from the forest plot when the outcome was reported only as within-group change, percentage change, standardized effect, or in incompatible units.

Study selection, extraction, and appraisal

Titles and abstracts were screened against the population, intervention/exposure, comparator, outcome, and study-design framework. Full texts were then assessed for design, country, sample size, stroke chronicity, baseline motor status, intervention frequency-intensity-time-type, comparator, mitochondrial or neuroplasticity measurement, functional endpoint, adverse events, and numerical effect. Priority was given to multicenter randomized trials, prespecified primary outcomes, intention-to-treat analyses, blinded assessors, validated outcome measures, and confidence intervals. Risk of bias was judged qualitatively using Cochrane RoB 2 domains for trials, ROBINS-I concepts for nonrandomized studies, and AMSTAR 2 concepts for reviews. The certainty of mechanistic claims was downgraded for small samples, indirect blood-cell proxies, cross-sectional design, or inconsistent measurement timing.

Statistical analysis

Published mean differences and 95% confidence intervals were extracted without re-estimating participant-level data. Standard errors were reconstructed as SE=(upper CI-lower CI)/(2 x 1.96), and two-sided z statistics were calculated as effect/SE for a consistency check. Forest-plot markers were centered on the reported mean difference and horizontal lines represented 95% confidence intervals. A common pooled estimate, Cochran Q, and I2 were intentionally not calculated because the plotted evidence includes both individual trials and meta-analytic summaries, uses different active comparators, and is therefore statistically non-independent. Statistical significance was interpreted at $P<0.05$, but clinical interpretation emphasized magnitude, durability, safety, and the minimally important context rather than P values alone. The circular diagram was a descriptive evidence map: each therapeutic target mentioned as a distinct actionable domain in the Results was coded once per domain statement and summarized as counts and percentages; it is not a patient-level analysis.

Results

Evidence profile

The retained evidence comprised recent randomized exercise trials from Canada and the United States, a multicenter Norwegian trial, mechanistic studies from the United States and Spain, and

systematic reviews from Australia, Belgium, Spain, and international groups. Samples ranged from five participants in preliminary mitochondrial biomarker work to hundreds of participants in meta-analyses. Most intervention evidence concerned ambulatory chronic stroke, whereas severe paresis and the early subacute phase remained underrepresented. The main sources of bias were limited blinding, small mechanistic samples, variable comparator intensity, and selective biomarker timing.

Table 1. Phenotype-to-target framework for personalized post-stroke rehabilitation.

Target phenotype	*Candidate measure*	*Rehabilitation lever*	*Decision signal*
Low oxidative reserve	*CPET VO2peak; NIRS recovery; fatigue*	*Aerobic intervals or continuous training*	*Progress intensity when symptoms and recovery are stable*
Paretic muscle deconditioning	*Strength; ultrasound; EMG; gait economy*	*Progressive resistance and task loading*	*Increase load when movement quality is preserved*
Weak voluntary recruitment	*FMA; motor evoked potentials; EMG*	*FES/NMES paired with active task practice*	*Use stimulation when intent-execution coupling is limited*
Plasticity-responsive profile	*BDNF trend; corticospinal integrity; learning slope*	*High-repetition, salient task practice*	*Advance complexity when retention and transfer improve*
Low systemic reserve	*Blood pressure; ECG; sleep; nutrition; comorbidity*	*Recovery optimization and lower initial dose*	*Escalate only after safety and adherence thresholds are met*

Mitochondrial and microvascular dysfunction

In 15 chronic stroke survivors and 15 matched controls, the paretic tibialis anterior had a slower resting oxygen-desaturation rate than control muscle (-0.12+/-0.04 versus -0.25+/-0.18% s-1; P=0.007) and slower post-occlusion resaturation than the nonparetic limb (1.60+/-1.11 versus 3.13+/-2.08% s-1; P=0.01) [3]. These findings support a combined impairment of oxidative utilization and endothelial reactivity, with microvascular function correlated with paretic strength. A 2025 Spanish pilot study of five chronic stroke patients found reduced pre-intervention electron-transport-chain activity in peripheral blood cells and significant increases in complexes and related enzymes after 12 sessions of FES plus exercise [7]. The latter is hypothesis-generating because the sample was very small, uncontrolled, and based on circulating-cell proxies rather than muscle biopsy.

Neuromuscular plasticity and training intensity

Exercise can couple peripheral metabolic stress to central plasticity through lactate signaling, cerebral perfusion, BDNF release, afferent input, and repeated motor-network activation. An Australian meta-analysis of 17 studies (687 participants) reported increased BDNF after a single high-intensity session (MD 2.49 ng/mL, 95% CI 1.10-3.88) and after high-intensity aerobic programs (MD 3.42 ng/mL, 95% CI 1.92-4.92) [5]. High-intensity walking also produced a 44-m greater 6-minute walk gain than moderate aerobic training after 12 weeks (95% CI 14-74) in a US multicenter trial [6]. These signals favor sufficient physiological challenge, while emphasizing screening and graded progression.

Exploratory quantitative synthesis

Four estimates using VO2peak in the same unit were plotted. Canadian and Toronto trials found short-term between-group advantages of 1.81 (95% CI 0.58-3.04) and 3.20 (95% CI 1.50-4.80) mL kg-1 min-1 for HIIT over MICT [8,9]. A 2026 randomized-trial meta-analysis reported MD 1.88 (95% CI 1.20-2.55) for HIIT versus MICT [10]. A Belgian-Canadian review of 38 trials reported MD 3.16 (95% CI 2.83-3.49) for aerobic or mixed training versus control [11]. All confidence intervals excluded zero, but the last estimate addresses a broader comparator and should not be interpreted as confirmation of the same treatment contrast.

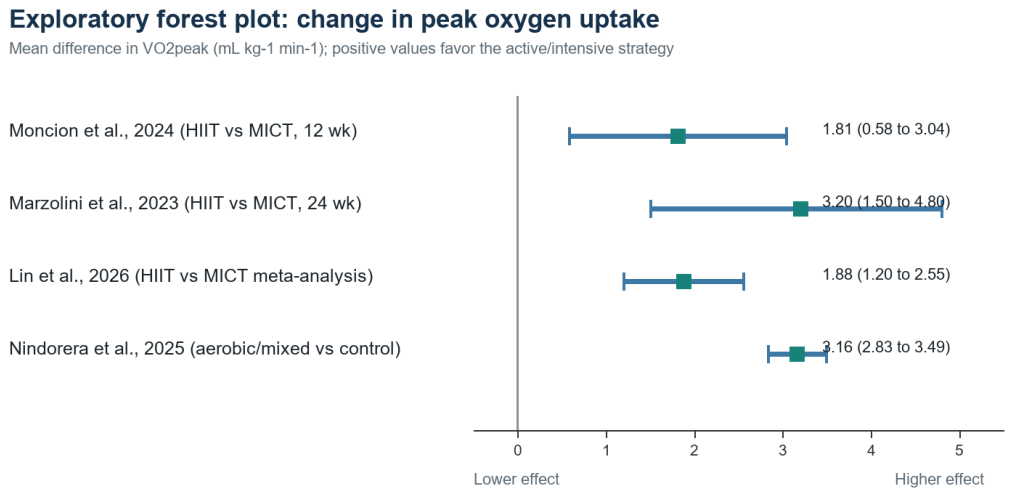

Figure 1. Exploratory forest plot of published mean differences in VO2peak. No pooled estimate was calculated because trial and review estimates are non-independent and comparators differ.

Therapeutic target distribution

Seventeen actionable target mentions were coded across the evidence map. Aerobic bioenergetics was most frequent (5/17), followed by task-specific plasticity (4/17), strength or NMES/FES (3/17), monitoring biomarkers (3/17), and recovery or nutrition (2/17). This distribution reflects the breadth of the reviewed Results and not comparative efficacy.

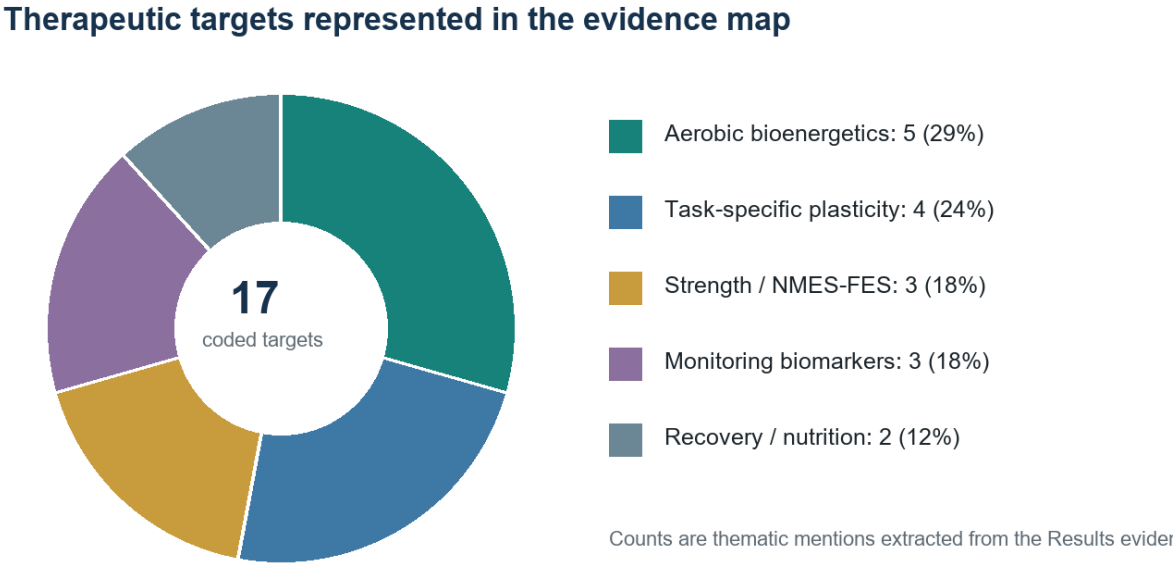

Figure 2. Descriptive distribution of therapeutic targets derived from the Results evidence map.

Discussion

The central finding is that mitochondrial and neuromuscular targets should be treated as an integrated system. Low oxidative capacity limits repetitions, walking speed, and motor-learning dose; inefficient motor recruitment increases the oxygen cost of movement; and inactivity further suppresses mitochondrial biogenesis. Conversely, appropriately dosed aerobic work can improve VO2peak and BDNF signaling, while task-specific practice, resistance loading, and FES convert physiological reserve into useful motor behavior. The therapeutic objective is not maximal intensity for every patient, but the highest repeatable stimulus that preserves safety, movement quality, and next-session readiness.

A practical personalized sequence begins with phenotyping. Cardiopulmonary exercise testing or a symptom-limited field test estimates systemic reserve. NIRS, where available, can characterize local oxygen utilization and reperfusion; strength, EMG, gait economy, FMA, and corticospinal tract measures define the neuromuscular bottleneck. Patients with adequate voluntary control but low aerobic reserve may start with monitored cycling or treadmill intervals. Those with severe recruitment failure may require NMES/FES synchronized with attempted movement and task practice before vigorous whole-body

training becomes feasible. Resistance training is prioritized when force production and muscle mass are dominant constraints. Sleep, protein-energy intake, glycemic control, spasticity, pain, and depression are parallel modifiers of mitochondrial adaptation and adherence.

Treatment should be adaptive. Intensity can be prescribed by heart-rate reserve, VO2 reserve, ventilatory threshold, perceived exertion, or workload when autonomic or beta-blocker effects make heart rate unreliable. Reassessment every 2-4 weeks should examine learning slope, fatigue, gait quality, blood pressure, adverse events, and attainment of target intensity. A plateau with good tolerance suggests progression of workload, complexity, or volume; a plateau with prolonged fatigue suggests recovery optimization or a switch in modality. Connectome-based prediction and blood neuroplasticity markers are promising stratifiers, but currently complement rather than replace clinical examination [12,13].

Conclusion

Mitochondrial dysfunction and neuromuscular plasticity are complementary targets for precision rehabilitation after stroke. Recent evidence supports intensity-monitored aerobic training for improving VO2peak and BDNF-related plasticity, while resistance training, task-specific repetition, and FES address peripheral weakness and impaired recruitment. Personalization should match the intervention to cardiovascular reserve, oxidative capacity, corticospinal integrity, motor severity, fatigue, and functional goals. The next generation of trials should combine standardized functional outcomes with repeated NIRS, muscle or blood bioenergetic markers, and neurophysiological measures to identify responders and define biologically effective dose.

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STATE-OF-THE-ART HIGH-TECH RADIATION THERAPY IN CLINICAL ONCOLOGY

Arman Khozhayev
Professor of the S.N. Nugmanov Department of Oncology, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
Cem Parlak
Head of the Tomotherapy Department, Tomotherapy Center «ALMA MEDICAL GROUP», Almaty, Kazakhstan
Madina Ismailova
Deputy Head of the Tomotherapy Department, Tomotherapy Center «ALMA MEDICAL GROUP», Almaty, Kazakhstan
Olzhas Sabyruly
Head Department of Radiology, «Regional Multidisciplinary Clinic» of the State Institution «Health Department of Zhetisu Region», Taldykorgan, Kazakhstan
Bakhtiyar Kussainov
Radiation Oncologist, «Regional Multidisciplinary Clinic» of the State Institution «Health Department of Zhetisu Region», Taldykorgan, Kazakhstan
Aizhan Abilkassymova
Oncologist, Balkhash Central District Hospital, Almaty region, Kazakhstan

Abstract

This scientific and analytical work examines current advances in radiation therapy and their impact on the management of oncological diseases. The paper presents an overview of modern radiotherapy technologies, including intensity-modulated radiation therapy, magnetic resonance-guided radiotherapy, adaptive radiation therapy, proton beam therapy, particle therapy, and FLASH radiotherapy. Particular attention is given to the physical principles, clinical applications, advantages, and limitations of these innovative treatment approaches. The article also describes recent developments in medical imaging and adaptive treatment strategies that improve target localization and enhance the precision of radiation delivery while minimizing exposure to surrounding healthy tissues. Furthermore, the role of artificial intelligence, deep learning, and radiomics in automated contouring, treatment planning, and personalized radiation oncology is comprehensively discussed. Current evidence demonstrates that the integration of advanced imaging technologies and intelligent computational methods has the potential to improve treatment efficiency, accuracy, and clinical outcomes. Existing technical and clinical challenges associated with the implementation of these technologies are also highlighted. The findings indicate that continuous technological innovation is transforming radiation oncology toward more precise, individualized, and effective cancer treatment.

Keywords: *oncology, high-tech radiation therapy, ionizing radiation, radiomics, proton therapy, intensity-modulated radiation therapy, magnetic resonance-guided radiotherapy, adaptive radiation therapy, FLASH radiotherapy, artificial intelligence.*

Today, high-tech radiation therapy is one of the most promising areas in the treatment of patients with malignant neoplasms from various localizations of the oncological process. Radiation therapy is used both independently and as part of combined and complex treatment. At the same time, radiation therapy is often the main radical method of treating malignant tumors, for example, for some forms of head and neck tumors, skin cancer, etc. The proportion of patients requiring radiation therapy is steadily growing. At the same time, the problem of improving the quality of radiation therapy is becoming increasingly urgent. It should be noted that the effectiveness and acceptability of a radiation therapy regimen depends both on the use of modern high-tech equipment and on the adequate implementation of preventive measures to reduce the consequences of radiation damage to irradiated healthy organs and

tissues while maintaining their normal functioning. At the same time, the role of qualified medical personnel conducting radiation therapy is difficult to overestimate, and well-coordinated professional work of the team is the key to good treatment results for cancer patients in need of this treatment method [1,2].

Ionizing radiation is radiation that, when interacting with a medium, transforms neutral atoms into ions - particles carrying positive or negative electrical charges. All radiation that, when interacting with the environment, is capable of causing ionization of atoms (i.e., their decay into oppositely charged particles - ions), including atoms that make up the human body, is called ionizing. Ionizing radiation is of two types: 1) quantum (electromagnetic) - consists of photons: a) X-ray radiation (bremsstrahlung and characteristic); b) gamma radiation; 2) corpuscular - consist of particles (beams of particles: electrons, protons, neutrons, mesons, etc.). The radiosensitivity of cells, tissues and organs is usually called their reaction to ionizing radiation. The most sensitive to radiation are hematopoietic tissue, the glandular apparatus of the intestines, the epithelium of the gonads, the epithelium of the skin and the bags of the lens of the eye. However, functional disorders can also be observed in other tissues and organs at relatively small doses, for example, in nervous tissue. The radiosensitivity of tissues and cells is not a constant value; it can change depending on the state of the body, and under the influence of a number of factors that are studied by clinical radiobiology [3].

In radiation oncology, sources of ionizing radiation and devices created on their basis are divided into: 1) radioactive substances: a) gamma installations (for long-distance and short-distance irradiation); b) radioactive drugs (closed, open); 2) charged particle accelerators: a) linear electron accelerator; b) cyclic electron accelerator (betatron); c) X-ray therapy units (for long-distance and short-distance irradiation).

At the same time, radioactive substances are substances capable of spontaneously and continuously emitting corpuscular or electromagnetic radiation. In medical practice, radioactive substances are used as radiation sources in γ-installations or in the form of radioactive drugs. γ-installations are of two types: type 1 - for long-distance irradiation - long-focus – tele – γ-installations and type 2 - for close-range irradiation - close-focus - short-focus γ-installations. Type 1 γ-installations are charged with a large amount of radioactive substance and are designed to expose γ-radiation to foci located deep in the human body. Most often the emitter is radioactive Cobalt. It emits β-radiation (with a particle energy of 0.318 MeV, which is completely absorbed by a special filter) and γ-rays with energies of 1.17 and 1.33 MeV. There are γ-installations charged with radioactive Iridium, producing γ-radiation with an energy of 0.88 MeV, radioactive Cesium with a photon energy of 0.66 MeV, etc. Type 2 γ-installations are charged with a small amount of radioactive Cobalt (Co60) or radioactive Cesium (Cs137). Devices of these types are intended for therapeutic effects on lesions located no deeper than 5 cm from the surface of the body. As for radioactive drugs, some of them are radioactive substances enclosed in various shells and filters that prevent direct contact of the isotope with human tissue and do not enter into the metabolic processes of the body (closed sources of radiation). In accordance with various purposes, different types of preparations are made - tubes, needles, disks, beads (in which the radioactive isotope is located inside a sealed metal channel or container with two walls - sealed glass inside and metal outside), nylon threads with a radioactive charge, radioactive gauze and bandages, catheters with inflatable balloons into which a solution of a radioactive substance is poured, charged particle accelerators, and γ-therapeutic devices. Another part of radioactive drugs are solutions of radioactive substances or various chemical compounds that contain radioactive atoms. These compounds or solutions, after being introduced into the patient's body for the purpose of diagnostic studies or for irradiating pathological foci, enter into the metabolic processes (metabolism) of the body (open sources of radiation). In addition, a radioactive isotope can be placed in hollow catgut threads, which are sewn into the stump of an organ resected for a malignant tumor, and as they are absorbed, the radioactive substance enters the tissue (a conditionally closed source of radiation). Charged particle accelerators (X-ray units, linear accelerators and cyclic accelerators - betatrons). The starting point of the accelerator is a source of charged particles. The source of electrons can be any heated piece of metal, from which electrons constantly jump out and immediately return. In this case, two problems are automatically solved: particles can be kept in orbit for as long as necessary, and the accelerating electric field does not have to be large (a thousand passes through a potential difference of one kilovolt is equivalent to a megavolt linear generator) [3].

Now, regarding radiation protection. Radiation protection is one of the areas of medical radiobiology. This is a set of measures aimed at protecting living organisms from ionizing radiation, as well as finding ways to reduce the damaging effects of ionizing radiation [3,4].

What means of radiation protection are used? Means of protection are divided into collective and

individual. Collective protective equipment is divided into protective equipment: 1) means of protection against external radiation include protective screens and devices for remote work; 2) means of protection against internal radiation used when working with open sources of ionizing radiation, depending on the method of protection, are divided into the following groups: sealing devices (chambers, protective boxes, capsules); protective coatings (paint and varnish, polymer, metal, ceramic, glass); air and liquid purification devices (ventilation, filtering, condensation, fixing) and decontamination means (decontamination solutions and decontamination dry materials); 3) means of protection against combined radiation include a combination of devices for protection from both external and internal radiation; 4) general purpose protective equipment includes automatic control, blocking and alarm devices; remote control devices; means of protection during transportation and temporary storage of radioactive substances (containers and packaging); safety signs (radiation hazard sign, warning signs); containers for solid and liquid radioactive waste [3].

The main factors (means) of protection are stationary and non-stationary devices. Stationary devices are fixed structures - walls, ceilings, security doors, observation windows, walls for local protection. They provide protection from direct and scattered radiation to all persons located in rooms adjacent to the radiation source. Based on the power of the installations and radioactive substances used, the thickness of all protective devices is calculated. Brick, concrete, barite concrete, and barite plaster are used to make walls. Barite contains barium, so it absorbs ionizing radiation to a large extent. Doors to radiology rooms are lined with sheet lead or made of metal. Thick leaded glass is inserted into the observation windows. Non-stationary (moving) protective devices are movable devices designed to protect personnel and patients located in the same premises where radiation sources are located (protective screens, casings in which radioactive drugs or X-ray tubes are placed, safes, containers, protective screens, devices for individual protection: special aprons made of leaded rubber, protective skirts, gloves, caps, sheets of leaded rubber or special lead plates, special remote tools - syringes, pipettes) [3].

Radiation therapy works by using ionizing radiation to damage the DNA of cancer cells, preventing them from dividing and causing them to die. There are different types of radiation therapy, depending on the type of radiation and how it is delivered:

1. X-ray therapy - the use of x-rays.

2. γ-therapy - the use of γ-rays, usually from radioactive sources.

3. Proton therapy - the use of protons, providing a more precise effect on the tumor.

4. Therapy using heavy ions - ions of carbon and other elements, providing high efficiency in the treatment of resistant tumors.

Classification of radiation therapy methods [5]: I. External beam radiation therapy: 1) X-ray therapy; 2) remote γ-therapy with traditional two-dimensional irradiation; 3) radiation therapy with high-energy X-ray bremsstrahlung (two-dimensional radiation therapy (conventional); three-dimensional radiation therapy; three-dimensional conformal radiation therapy (3DCRT); intensity-modulated radiation therapy (IMRT); image-guided radiation therapy (IGRT); four-dimensional radiation therapy (4D RT); stereotactic radiosurgery (SRS); stereotactic radiation therapy (SRT); 4) radiation therapy with charged particles (β-, a-, protons, neutrons , ions, etc.); II. Contact radiation therapy (brachytherapy): 1) application radiation therapy; 2) intracavitary radiation therapy; 3) interstitial radiation therapy.

Technological advances in radiation therapy clearly include IMRT. IMRT is a high-tech technique of external three-dimensional radiation therapy used to treat patients with malignant and some types of benign tumors, allowing ionizing radiation to more precisely adapt to the tumor.

In this case, a very precise distribution of the dose of ionizing radiation is created around a target (tumor) of complex shape, its entire volume is outlined and painted over with a high dose of radiation. The use of IMRT makes it possible to minimize radiation exposure to healthy tissues and critical organs by creating a radiation field of any desired shape and delivering irradiation at different intensities during the same session [6].

IMRT is a technique in which the intensity of the beam is modulated during the treatment process. This allows high doses of radiation to be delivered directly to the tumor while minimizing exposure to surrounding healthy tissue. The benefits of IMRT include improved tumor control and reduced side effects.

When performing IMRT of tumors of various localizations, external beam radiation therapy is used, and the indications for its implementation are: 1) the presence of a malignant neoplasm of any localization with mandatory morphological verification of the diagnosis after surgical treatment or biopsy; 2) the presence of a malignant neoplasm of any location or benign tumors of the central nervous system without morphological verification with diagnosis based on clinical and instrumental research methods

[Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography Computed Tomography (PET-CT)]; 3) the presence of a secondary (metastatic or without a primarily defined focus) tumor with morphological confirmation of the diagnosis after surgical treatment or open biopsy, or the absence of morphological confirmation of metastasis, but the presence of histological verification of the primary focus.

At the same time, the following requirements are imposed on the qualifications of medical personnel: 1) personnel working in radiation therapy departments (radiology departments) of medical organizations providing oncological care to the population must have the appropriate knowledge and qualifications, confirmed by the necessary documents, and belong to group A personnel, and have access to work with sources of ionizing radiation, as well as unexpired certificates for completing radiation safety courses; 2) a specialist with a certificate in the specialty «Radiation Therapy» (Radiation Oncology) with at least 5 years of experience in the specialty, advanced training in high-tech methods of radiation therapy for at least 240 hours over the last 5 years; 3) a specialist with a higher education in physics and/or higher technical education with at least 3 years of experience in the specialty, and at least 2 years of experience working with linear (cyclic) accelerators.

Further, as regards the algorithm for carrying out the medical procedure/intervention IMRT. The standard IMRT procedure includes the following main steps:

Stage 1: Prescribing a course of IMRT indicating the radiation treatment plan. The radiation therapist (radiation oncologist) determines the indications for radiation therapy and prescribes a course of IMRT indicating the radiation treatment plan, in which it is necessary to indicate Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Planning Target Volume (PTV), Organs At Risk (OAR). Depending on the fractionation mode, Single Focal Dose (SFD) from 1.6 Gy to 8.0 Gy per week Total Focal Dose (TFD) from 8.0 to 84.0 Gy 5 fractions per week in a continuous or split course. The patient is positioned therapeutically on the deck of the CT table using fixing individual thermoplastic masks, special supports for the legs, head, and vacuum bags. The type (brand) of the linear accelerator is determined.

Stage 2: Pre-radiation topometric preparation on an X-ray simulator and/or CT scanner with a virtual simulation function. A radiation therapist (radiation oncologist) and a radiation diagnostics doctor (radioisotope diagnostics) conduct pre-radiation topometric preparation on an X-ray simulator using Cone Beam Computed Tomography (CBCT) and/or a CT tomograph with the obligatory performance of: 1) positioning - selection of the patient's position; 2) fixation with individual thermoplastic masks; 3) applying topographic marks; 4) transfer of data in Digital Imaging and Communications in Medicine (DICOM) format to the dosimetric planning system.

Stage 3: Computerization of radiation images: 3-D reconstruction, spatial registration of images, volume contouring for IMRT with the obligatory setting of tolerance of critical organs. A medical physicist (radiology physicist) together with a radiation therapist (radiation oncologist) perform computerization of radiation images - 3-D reconstruction by creating a 3-dimensional reconstruction of the area of the body of interest according to a series of CT slices obtained under identical conditions of patient positioning and fixation, reproducible during topometric preparation and further daily irradiation sessions. Next, together with the participation of a radiation diagnostics (radioisotope diagnostics) doctor, spatial co-registration of images (matching, fusion) is carried out - combining digital data in DICOM format CT with MRI or PET-CT to obtain accurate information about the spread of the tumor and organs at risk, indicating them tolerance according to international protocols: Radiation Therapy Oncology Group (RTOG)/ European Organisation for Research and Treatment of Cancer (EORTC), Tolerance Dose 5/5 (TD5/5) and Tolerance Dose 50/5 (TD50/5), Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), etc.

Stage 4: Dosimetric planning IMRT: 1) creation and selection of dosimetric plans with their approval; 2) an independent system for checking dosimetric plans - quality control; 3) verification of the dosimetric plan.

After receiving all the contours, the medical physicist (radiology physicist) conducts IMRT dosimetric planning - calculating the radiation therapy plan to achieve optimal dose distribution within the tumor, with maximum protection of critical (healthy) organs/tissues surrounding the tumor. Together with a radiation oncologist, a clinical analysis of the selected and alternative dosimetric plans is carried out - joint discussion and approval of the optimal dosimetric plan, by comparing the dose distribution with the shape of the planned target volume and critical organs and assessing dose-volume histograms. Additionally, an independent system of verification of the selected dosimetry plan (quality control) is carried out by a medical physicist (radiology physicist) who did not participate in their planning: each IMRT exposure plan is re-checked on an independent dosimetry planning system and an independent Monitor Units

check is performed. As well as verification of the dosimetric plan of radiation therapy, in order to reduce the discrepancy in dosimetric and geometric parameters between the actual and planned treatment of the patient before the start of radiation therapy. Each treatment plan is tested on a linear accelerator using an array detector + a cylindrical phantom or on an array with plastic plates, or by portal dosimetry. After completing all dosimetric procedures, the finished plan is tested on the patient. A radiation therapist (radiation oncologist) performs the so-called procedure of simulation (imitation) of radiation treatment - checking the geometric parameters of the dosimetric plan of radiation treatment on the patient's body under fluoroscopic control of the simulator with correction of topographic marks.

Stage 5: Implementation of the IMRT plan: carrying out radiation procedures, with mandatory portal megavoltage or kilovoltage imaging (positioning check and verification) before the radiation therapy session according to the drawn up scheme. After all the parameters planned and obtained during the simulation coincide with the correction of skin marks, the radiation therapist (radiation oncologist) together with the medical physicist (radiology physicist) and the nurse (laboratory assistant) begin to implement the approved IMRT plan. Before each patient is positioned for an irradiation session, it is necessary to conduct portal megavoltage imaging, which allows for the highest possible positioning accuracy and verification using Electronic Portal Imaging Device (EPID). After correcting possible inaccuracies and errors in the patient's positioning, the IMRT procedure for tumors of the central nervous system is performed. The presence of a radiation therapist (radiation oncologist) and a medical physicist (radiology physicist) is mandatory during the first treatment positioning of the patient; subsequent treatment placements of the patient are allowed only by a specially trained and trained nurse to work on linear accelerators. It is mandatory to fill out: radiological cards with completion at the end of the dispensed radiation doses for all volumes, a quality control report protocol for visual verification using megavoltage imaging on EPID.

The indicators of the effectiveness of the procedure are as follows. The effectiveness of IMRT is assessed after completion of the procedure - a full course of radiation therapy based on an analysis of the objective effect criteria on the Response Evaluation Criteria In Solid Tumors (RECIST) scale in accordance with World Health Organization and EORTC recommendations, taking into account the objective and subjective effects obtained during clinical examination, control laboratory and instrumental studies: complete regression - 100 % disappearance of tumor; partial regression – reduction in size by 50% or more; stabilization of the process – reduction in tumor size by less than 50%; progression is an increase in tumor size by more than 25% [6].

Otazo R. et al. [7], in their work, consider MRI-guided radiation therapy as a new paradigm for adaptive radiation therapy. The paper's main contribution is that it sees MRI navigation not simply as an improvement in imaging, but as a platform to change the entire logic of radiotherapy. The authors emphasize that MRI provides superior soft tissue contrast compared to CT, which is especially important for tumors in the abdomen, pelvis and other anatomically complex areas. This allows more accurate identification of the target and risk organs during treatment. The article is important because it connects imaging, motion management and biological adaptation. The authors describe offline and online MRI-guided workflows and show that online adaptation can compensate for daily anatomical changes before dose delivery. From an expert perspective, the publication demonstrates that MR-guided radiotherapy (MRgRT) is not simply a more accurate version of IGRT; it is a technological step toward personalized radiotherapy in which the treatment plan may be adjusted according to the patient's actual anatomy on the day of irradiation. The work also identifies barriers such as cost, workflow complexity and the need for multidisciplinary collaboration. Therefore, this source is fundamental for understanding why MRgRT is considered one of the leading modern aspects of high-tech radiation therapy.

Kurz C. et al. [8] analyze the medical physics challenges that arise when MRI is integrated into external beam radiotherapy. Unlike clinical reviews that emphasize benefits, this publication provides a technically rigorous discussion of the limitations that must be solved before MRgRT can be safely used. The authors focus on magnetic-field effects, dose calculation accuracy, image distortions, geometric fidelity, quality assurance and commissioning of MR-linac systems. This work is especially relevant because high-tech radiotherapy depends on the reliability of physical dose delivery. The presence of a magnetic field can influence secondary electron trajectories and modify dose distributions, particularly near tissue-air interfaces. The authors show that MRgRT requires careful adaptation of dosimetric models and verification procedures. From an expert point of view, this source adds balance to the review: it demonstrates that advanced technology increases clinical opportunity but also increases technical responsibility. The paper supports the idea that the future of radiotherapy will require close cooperation between radiation oncologists, physicists, dosimetrists and engineers. Therefore, it is a key source for understanding the

infrastructure and physics behind safe MR-guided high-tech treatment.

Glide-Hurst C.K. et al. [9] provide a comprehensive review of adaptive radiation therapy strategies and technical requirements. The work is valuable because it systematizes Adaptive Radiation Therapy (ART) into practical workflows and explains what is required for safe clinical implementation. The authors discuss online, offline and real-time adaptation, emphasizing that ART is necessary because tumors and normal tissues are not static during treatment. Tumor regression, weight loss, organ filling and respiratory motion can all alter the original dose distribution. The expert significance of this source lies in its focus on operational and quality assurance aspects. The authors analyze image quality, deformable image registration, dose accumulation, contour propagation, plan adaptation and staffing requirements. This distinguishes the paper from purely conceptual reviews. It shows that ART is not only a technological feature but a complex clinical process requiring validated software, trained personnel and clear decision-making criteria. In the context of high-tech radiotherapy, this article demonstrates that precision cannot be achieved solely by advanced equipment; it also depends on adaptive workflows and quality management. The source supports the conclusion that adaptive radiotherapy is becoming one of the foundations of personalized radiation oncology.

Hoffmann A. et al. [10] investigate the concept of MR-guided proton therapy, a technically ambitious combination of two major high-tech directions: MRI guidance and particle therapy. The article explains that proton therapy already offers a physical advantage through the Bragg peak, but that this advantage is highly sensitive to anatomical changes, tissue density variations and motion. MRI guidance could potentially improve target localization, motion management and adaptive proton planning. The publication is important because it highlights a future-oriented frontier rather than a fully established clinical routine. The authors discuss technical obstacles such as proton beam deflection in magnetic fields, integration of MRI into proton treatment rooms and the need for accurate MRI-based stopping power estimation. Expert analysis of this source shows that the next generation of proton therapy will likely depend on improved imaging and adaptation. The article also demonstrates that the more conformal a therapy becomes, the more vulnerable it is to anatomical uncertainty. Thus, MR-guided proton therapy illustrates the broader principle of high-tech radiotherapy: increased precision requires equally advanced verification and adaptation.

Pham T.T. et al. review MRI-guided proton therapy and focus on the potential clinical value of combining excellent soft-tissue visualization with the dosimetric advantages of protons [11]. The work emphasizes that tumor sites with substantial motion or daily anatomical variability could benefit most from this hybrid approach. Abdominal and pelvic tumors are especially relevant because conventional proton therapy may be affected by changes in organ filling, gas pockets and respiratory movement. The expert value of this source is its discussion of feasibility and translational barriers. The authors consider MRI-only planning, synthetic CT generation, proton range estimation and the technical implications of magnetic fields on proton dose delivery. In the broader context of high-tech radiotherapy, the article demonstrates that the future may involve convergence of technologies rather than isolated innovations. MRI guidance, adaptive workflows and particle therapy are not separate fields; they may become integrated components of one precision platform. This source therefore strengthens the overall review by showing how image guidance and proton therapy can be combined to address limitations of each modality.

Keall P.J. et al. [12] present an authoritative review of integrated MRgRT, describing both the opportunities and the challenges of this technology. The authors explain that MRI guidance enables more precise targeting during treatment delivery and can reduce unnecessary irradiation of surrounding normal tissues. The review also emphasizes that anatomy and physiology are dynamic, which makes static planning insufficient for many clinical scenarios. The major contribution of this work is its broad strategic perspective. It discusses real-time imaging, adaptive replanning, functional MRI, tumor response monitoring and the possibility of targeting biologically aggressive tumor subregions. From an expert standpoint, this source extends the discussion beyond anatomical precision. It suggests that MRI-guided therapy may support biologically adaptive radiotherapy, where treatment is modified according to functional or biological information during the course of care. At the same time, the authors identify barriers including workflow burden, cost, training and evidence generation. This makes the article highly relevant for a professor-level review because it combines clinical vision with practical realism.

Ladbury C. et al. provide a narrative review of clinical applications of MRgRT [13]. The authors focus on practical indications where MRgRT is most likely to offer meaningful benefit, including pancreatic cancer, liver tumors, prostate cancer, rectal cancer and gynecological malignancies. These tumors often involve soft-tissue targets, organ motion or proximity to radiosensitive structures. This publication is useful because it translates the technological advantages of MRgRT into clinical decision-making. The

authors emphasize that tumors with significant motion, tumors better visualized on MRI, cases requiring smaller margins and hypofractionated treatments are strong candidates for MR guidance. From an expert perspective, the article supports a selective rather than universal approach to MRgRT implementation. Not every patient requires MR-guided treatment, but selected patients may benefit substantially from improved visualization and online adaptation. The source therefore contributes to the review by connecting technology to patient selection, clinical workflow and expected benefit.

Zaki P. et al. [14] analyze proton beam therapy and MRgRT in the management of hepatocellular carcinoma. This source is clinically important because liver tumors are challenging for radiotherapy due to respiratory motion, limited liver tolerance and proximity to gastrointestinal organs. The authors show that both proton therapy and online adaptive MRgRT may address these limitations by reducing unnecessary dose to normal liver, stomach and bowel. The expert contribution of this article lies in its disease-specific evaluation of high-tech radiotherapy. Rather than discussing technologies in abstraction, it shows how advanced external beam radiotherapy can expand indications for a tumor historically considered difficult to irradiate. Proton therapy can reduce integral dose to uninvolved liver, while MRgRT can improve motion management and daily adaptation. This combination of physical dose advantage and image-guided adaptation reflects the central trend in modern radiation oncology. The article supports the conclusion that high-tech radiotherapy is particularly valuable in anatomically complex cancers where conventional techniques are limited by toxicity.

McGarrigle J.M. et al. evaluate the FLASH effect and summarize preclinical evidence on ultra-high dose-rate radiotherapy [15]. FLASH radiotherapy is one of the most discussed emerging innovations because it may reduce normal tissue toxicity while preserving tumor control. The authors analyze experimental evidence and discuss the biological uncertainty surrounding the phenomenon. This source is important because it shows both the promise and immaturity of FLASH radiotherapy. Although preclinical results are encouraging, clinical translation requires reliable beam delivery systems, standardized dosimetry, appropriate fractionation models and better understanding of mechanisms. Expert assessment indicates that FLASH should be viewed as a frontier technology rather than an established clinical standard. Its relevance to high-tech radiation therapy lies in its potential to change the biological therapeutic window, not only the geometric precision of dose delivery. Therefore, the paper broadens the review from imaging and planning technologies toward radiobiological innovation.

Kim J.S. et al. review FLASH radiotherapy with emphasis on mechanisms and clinical translation [16]. The article defines FLASH radiotherapy as ultra-high dose-rate irradiation, commonly discussed at dose rates exceeding 40 Gy/s, and evaluates why this approach may widen the therapeutic window. The authors discuss potential mechanisms including oxygen depletion, immune modulation, radical chemistry and differences in normal tissue response. The publication contributes to the review by providing a translational perspective. It considers different radiation sources, including electrons, photons and protons, and explains why technical feasibility varies across modalities. From an expert standpoint, the source is important because it shows that implementation of FLASH is not only a biological question but also an engineering and dosimetry challenge. Reliable dose monitoring at extremely high dose rates is essential before broad clinical use. This article reinforces the general conclusion that modern high-tech radiotherapy is developing simultaneously in physics, biology, engineering and clinical medicine.

Of course, we cannot ignore the use of artificial intelligence (AI) in the application of high-tech radiation therapy to cancer patients.

Erdur A.C. et al. in their work [17] consider deep learning-based automatic segmentation for radiotherapy treatment planning. Auto-segmentation is one of the most clinically mature applications of AI in radiation oncology. Manual contouring of target volumes and OAR is time-consuming and subject to interobserver variability. Deep learning models can reduce workload and improve consistency, particularly for organs with clear anatomical boundaries. The expert relevance of this source is that it demonstrates how AI is becoming embedded into everyday radiotherapy workflows. Auto-segmentation directly affects treatment planning quality because contour accuracy determines dose optimization. The review also highlights limitations such as dataset bias, variable performance across institutions, need for clinician review and uncertainty in complex postoperative or distorted anatomy. Thus, the article supports a realistic view: AI can improve efficiency and standardization, but it cannot replace expert clinical responsibility. In the context of high-tech radiation therapy, this source shows that software innovation is as important as hardware innovation.

Kalsi S. et al. examine the evolving role of AI across the radiotherapy pathway [18]. The review covers applications in target segmentation, treatment planning, dose optimization, image analysis, outcome prediction and decision support. This broad scope is important because AI is not a single tool but a

set of methods that can influence nearly every stage of radiotherapy. From an expert perspective, the article is valuable because it links AI with workflow transformation. AI-based systems may reduce planning time, support standardization and help identify patients at increased risk of toxicity. However, the authors also emphasize validation, explainability, governance and integration into clinical practice. These concerns are crucial because radiotherapy is a high-stakes environment where algorithmic errors can affect patient safety. This source contributes to the overall review by showing that high-tech radiotherapy is increasingly computational and data-driven. The future role of AI will likely depend not only on model accuracy but also on regulation, quality assurance and clinician trust.

Chen M. et al. discuss radiomics and AI as tools for precision medicine in lung cancer treatment [19]. Radiomics involves extraction of quantitative features from medical images that may reflect tumor phenotype, heterogeneity and treatment response. When combined with AI, radiomics may help predict prognosis, radiosensitivity and risk of toxicity. The expert value of this source is that it connects radiotherapy with imaging biomarkers and personalized decision-making. Lung cancer is an especially relevant model because radiotherapy outcomes are affected by tumor motion, hypoxia, heterogeneity and differences in biological response. The review suggests that future radiotherapy may be guided not only by tumor size and location but also by quantitative imaging signatures. However, the authors also highlight challenges such as reproducibility, feature standardization, external validation and clinical interpretability. This source supports the conclusion that high-tech radiation therapy is moving toward biologically informed planning, where imaging data may influence dose selection and adaptation.

Summarizing the above, we can conclude that at the present stage of development of clinical radiation oncology, knowledge of algorithms and the use of high-tech radiation therapy methods makes it possible to provide effective full-fledged anti-cancer treatment to patients with malignant tumors with different localizations of the oncological process. This, in turn, makes it possible to improve long-term treatment results, disease prognosis and, most importantly, the quality of life of these patients.

The reviewed literature demonstrates that modern high-tech radiation therapy is no longer limited to improved beam shaping. It is becoming an integrated system that combines imaging, adaptation, automation, particle physics and biological modeling. MRgRT provides superior soft-tissue visualization and enables online adaptation. Adaptive radiotherapy addresses daily anatomical variability and turns treatment planning into a dynamic process rather than a one-time event. Medical physics studies emphasize that every technological advantage must be supported by rigorous dosimetry, image quality control and quality assurance. The sources on proton and particle therapy show that physical dose advantages can substantially improve normal tissue sparing, particularly in pediatric tumors and anatomically complex cancers. At the same time, these benefits depend on careful patient selection, robust planning and management of range uncertainty. The literature on artificial intelligence and radiomics demonstrates that the next stage of radiotherapy development will be increasingly data-driven. AI can support contouring, planning, prediction and adaptive workflows, but its safe use requires validation, transparency and clinician oversight. In connection with the above, it can be concluded that contemporary high-tech radiation therapy is moving toward personalized, adaptive and biologically informed cancer treatment. The reviewed sources collectively show that the main objective of modern radiotherapy is to improve the therapeutic ratio: increasing tumor control while reducing acute and late toxicity. The future of the field will depend on successful integration of MRI guidance, adaptive replanning, proton therapy, AI, radiomics and emerging radiobiological approaches such as FLASH therapy. Therefore, high-tech radiation therapy should be understood not as a single technology, but as a multidisciplinary platform that combines clinical oncology, medical physics, imaging science, computational medicine and radiobiology.

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