Научно-практический журнал для работников здравоохранения

Включён в Перечень ведущих рецензируемых периодических изданий ВАК Минобрнауки РФ

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

АПРЕЛЬ 2024 (№ 2(76))

УЧРЕДИТЕЛЬ И ИЗДАТЕЛЬ
Общество с ограниченной ответственностью «Синапс»
107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17
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Подписано в печать 25.03.2024 года
Тираж 3000 экземпляров.

Издание зарегистрировано в Федеральной службе по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор).

Свидетельство о регистрации
ПИ № ФС77-45961 от 26 июля 2011 г.

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Отпечатано в типографии «Onebook.ru»
ООО «Сам Полиграфист»
г. Москва, Волгоградский проспект, д. 42, корп. 5
www.onebook.ru

Журнал включен в Российский индекс научного цитирования (РИНЦ)

Статьи журнала представлены в Российской универсальной научной электронной библиотеке www.elibrary.ru

Подписной индекс в каталоге «Урал-Пресс Округ» 87732

DOI: 10.20514/2226-6704-2024-2

Scientific and practical journal for health professionals

Included the List of the Russian reviewed scientific magazines in which the main scientific results of theses on competition of academic degrees of the doctor and candidate of science have to be published.

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE
www.medarhive.ru
APRIL 2024 (№ 2(76))

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Signed for printing on 25.03.2024
Circulation 3000 exemplars

It is registered by state committee of the Russian Federation on the press

The certificate on registration of mass media ПИ № ФС77-45961, 26 July 2011

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Printed «Onebook.ru»
«Sam Poligrafist»
Moscow, Volgograd Prospect, 42-5
www.onebook.ru

The journal is included in Russia Science Citation Index (RSCI)

Journal data are published on website of Russian General Scientific Electronic Library www.elibrary.ru

Subscription index in the catalogue «Ural-Press Okrug» 87732

DOI: 10.20514/2226-6704-2024-2

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DOI: 10.20514/2226-6704-2024-14-2-85-95
УДК 616.13.002.2
EDN: CEXECW

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РОЛЬ МИКРОРНК И РЕТРОЭЛЕМЕНТОВ В ПАТОГЕНЕЗЕ АТЕРОСКЛЕРОЗА

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Role of MicroRNAs and Retroelements in the Pathogenesis of Atherosclerosis

Резюме

Атеросклероз является ведущей причиной сердечно-сосудистых заболеваний среди взрослого населения. Характерно значительное увеличение распространенности атеросклероза с возрастом, что свидетельствует о возможном влиянии на развитие болезни механизмов старения, в том числе изменений эпигенетических факторов, обусловленных регуляторным влиянием транспозонов. Триггерами атеросклероза являются также вирусные инфекции, которые способствуют активации ретроэлементов и стимуляции интерферонового ответа продуктами их экспрессии с развитием хронического воспаления, с нарушением регуляции генов иммунной системы, микроРНК и длинных некодирующих РНК. Перспективным направлением лечения атеросклероза является эпигенетическое воздействие на экспрессию специфических генов, вовлеченных в патогенез атеросклероза с помощью малых интерферирующих РНК. В данном отношении прошли клинические испытания препараты инклисиран и олпасиран, показавшие свою эффективность. Поэтому актуален поиск новых молекулярных мишеней в данном направлении, в качестве которых могут служить транспозоны, являющиеся источниками некодирующих РНК. Изменение активности ретроэлементов при старении оказывает глобальное регуляторное влияние на функционирование всего генома, способствуя развитию возраст-ассоциированной патологии. Анализ научной литературы позволил идентифицировать 29 произошедших от ретроэлементов микроРНК, изменения экспрессии которых определены как при старении, так и при атеросклерозе, что подтверждает предположение о роли активированных при старении ретроэлементов в развитии атеросклероза. Выявленные микроРНК предполагается использовать для таргетного воздействия с целью продления жизни и лечения атеросклероза.

Ключевые слова: *атеросклероз, микроРНК, ретроэлементы, таргетная терапия.*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 25.01.2024 г.
Принята к публикации 06.03.2024 г.

Для цитирования: Мустафин Р.Н., Галиева Э.А. РОЛЬ МИКРОРНК И РЕТРОЭЛЕМЕНТОВ В ПАТОГЕНЕЗЕ АТЕРОСКЛЕРОЗА. Архивъ внутренней медицины. 2024; 14(2): 85-95. DOI: 10.20514/2226-6704-2024-14-2-85-95. EDN: CEXECW

Abstract

Atherosclerosis is the leading cause of cardiovascular disease among adults. The incidence of atherosclerosis increases significantly with age, which indicates the possible influence of aging mechanisms on the development of the disease, including changes in epigenetic factors caused by pathological activation of transposable elements. Triggers of atherosclerosis are also viral infections, which promote the expression of retroelements that stimulate the interferon response with the development of chronic inflammation. Activated retroelements also alter the regulation of immune system genes and epigenetic factors, including the pathological production of microRNAs and long non-coding RNAs. A promising direction for

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atherosclerosis treatment is the epigenetic impact on the expression of specific genes involved in the pathogenesis of atherosclerosis using small interfering RNAs. In this regard, the drugs inclisiran and olpasiran have undergone clinical trials and have shown their effectiveness. Therefore, it is important to search for new molecular targets in this direction, which can serve as transposons, which are sources of non-coding RNAs. Changes in the activity of retroelements during aging have a global regulatory effect on the functioning of the entire genome, contributing to the development of age-associated pathology. An analysis of the scientific literature made it possible to identify 29 microRNAs derived from retroelements, changes in the expression of which have been identified both during aging and atherosclerosis. These microRNAs can be used as tools for prolonging life and treating cardiovascular pathology. The results obtained also indicate that retroelements pathologically activated during aging cause the development of atherosclerosis.

Key words: *atherosclerosis, microRNAs, retroelements, targeted therapy.*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 25.01.2024
Accepted for publication on 06.03.2024

For citation: Mustafin R.N., Galieva E.A. Role of MicroRNAs and Retroelements in the Pathogenesis of Atherosclerosis. The Russian Archives of Internal Medicine. 2024; 14(2): 85-95. DOI: 10.20514/2226-6704-2024-14-2-85-95. EDN: CEXECW

AS — atherosclerosis, AS PLEA — atherosclerosis of peripheral lower extremity artery, VSMC — vascular smooth muscle cell, RE — retroelements, EC — endothelial cells

Introduction

Atherosclerosis (AS) is the leading cause of cardiovascular diseases globally. AS is characterised by a long-lasting latent period and frequently involves more than one vascular bed. The key clinical manifestations of the disease are AS with involvement of coronary, carotid arteries, peripheral lower extremity arteries (AS PLEA), etc., ischemic heart disease and cerebral ischemia. Fat deposits on arterial walls gradually develop into sebaceous cysts and distinctive plaques, the quick rupture of which causes local thrombosis and partial or complete occlusion of the involved artery [1]. The global incidence of AS PLEA (from the iliac segment to feet) has risen by 45 % over the period from 2000 to 2015 and reached 5.6 % of the adult population globally (7.4 % — in high-income nations and 5.1 % — in low- and medium-income nations) [2]. IHD-caused mortality in Eastern Europe, including Russia, was 434 per 100,000 for men and 235 per 100,000 for women; while the rate of deaths from ischemic stroke was 138 per 100,000 of population in Russia. In addition to environmental factors, such as smoking, unhealthy diet with dyslipidemia and obesity [1], ageing and genetics have an important role to play in aetiopathogenesis of AS [3]. AS development is facilitated by kidney diseases due to faster calcification both of vessel intima (resulting in calcium deposition in atheromatous plaque) and of the middle layer (with an increase in the vessel rigidity) [1]. Major contributors (as compared to IHD) to the development of AS PLEA are smoking and type 2 diabetes mellitus. However, two thirds of patients with AS PLEA also have IHD and cerebral ischemia, evidencing the systemic nature of vessel involvement. A simple and reliable test to diagnose AS PLEA is the ankle-brachial index, which is calculated by dividing ankle systolic arterial pressure by shoulder systolic pressure [3].

According to results of meta-analyses, peripheral atherosclerosis is associated with allelic variants of *SYTL3* (rs2171209), *TCF7L2* (rs290481), *CYP2B6* [3]. Ischemic heart disease is associated with polymorphisms of 57 various genes [4]. Cerebral ischemia is associated with allelic variants of *VCAM1, LAMC2, GP1BA, PROC, KLKB1, F11,* which are planned to be used in the management of the disease [5]. However, it is impossible to explain the role of these numerous genes in the development of AS and to use them as targets for the target therapy. A study of epigenetic mechanisms of AS, which are reversible and can be efficiently corrected with the help of non-coding RNA (ncRNA), would be more promising. The epigenetic factors include DNA methylation, histone modification and RNA interference using ncRNA. During the ontogeny, the epigenetic factors are regulated by transposons, which include retroelements (RE) and DNA transposons [6]. A comparative study conducted in 2022 to study the epigenetic factors in samples obtained from patients with AS and healthy controls showed 47 activated (hypomethylated) and 90 inactive (hypermethylated) genes in AS, as well as 10 key AS genes (*TCF7L2, CACNA1C, NRP1, GABBR2, FANCC, DCK, CCDC88C, TCF12, ABLIM1, PBX1*), differentially expressed under the influence of microRNA and abnormal methylation [7]. AS development is facilitated by age-associated vascular wall inflammation [8], whereas ageing is associated with abnormal activation of HERV (human endogenous retroviruses) RE [9] and LINE-1 (long interspersed nuclear elements-1) [10], the products of transcription and translation of which stimulate interferon hyperproduction, causing chronic inflammatory processes in the body [9, 11]. The role of transposons in the initiation and development of AS is a result not only of interferon-mediated inflammation, but also of the participation in the immune system functioning.

An evidence of this can be formation of RAG1 and RAG2 recombination from transposons necessary for V(D)J [12], use of ERV as HLA-G gene enhancers [13] and interferon-inducible genes (thus forming transcriptional networks for interferon response [14]). Meta-analyses demonstrated the role of RE dysregulation in an autoimmune pathology [15], which is associated with the development of AS [16].

AS presents with persistent inflammation as a result of polarisation of AS-associated macrophages from anti-inflammatory (M2-like) to pro-inflammatory (M1-like) macrophages under the influence of epigenetic drug resistance factors. Since macrophages are important for the organisation of the entire process of AS development — from initiation to plaque rupture — they are called AS-associated macrophages. Since AS presents with persistent inflammation, modern therapies, including statins, ACE inhibitors, beta blockers and aspirin, have no effect on disease progression, because they do not specifically affect macrophages and their polarisation [17]. HERV-K102 are expressed by activated monocytes and move to vacuoles connected to their surfaces, making the cells look foamy. HERV-K102 are released only during macrophage lysis. HERV-K102 protect human cells against viral infections and malignancies [18]. Since clinical trials demonstrate that HIV, HSV-1 and HSV-2, hepatitis C (HCV) and B, cytomegalovirus (CMV), T-cell leukaemia and papilloma (HPV), flu (similar to those described in the systemic review [19]) contribute to the development of AS, HERV-K102 hyperproduction to protect the cells [18] can cause impaired gene expression in macrophages, leading to a pathology and involvement in AS pathogenesis [20]. REs are activated by stress factors [21].

Transposons regulate gene expression during human ontogeny [22], acting as drivers of epigenetic regulation [6], because they are sources of ncRNA, such as microRNA [23] and long ncRNA [24, 25]. Therefore, changes in expression of specific mcRNA in AS can represent RE dysregulation in these processes (Fig. 1). At the same time, ncRNA is not only involved in post-transcription regulation of gene expression, but also is a key driver of DNA and histone modification [6] due to the mechanism of RNA-directed DNA-methylation (RdDM). This phenomenon, which was first observed in plants, has been found in humans as well [26]. Over the last decades, new methods to impact the inflammation in AS have been developed, such as blocking the recruitment of inflammatory cells (using antagonists of chemokine receptors and adhesion molecules), neutralisation of pro-inflammatory factors (monoclonal antibodies to chemokines and cytokines), plaques stabilisation (matrix metalloproteinase inhibitors). However, almost all of them failed to demonstrate efficacy during preclinical and early clinical trials. For example, canakinumab, a monoclonal antibody to IL-1β, reduces

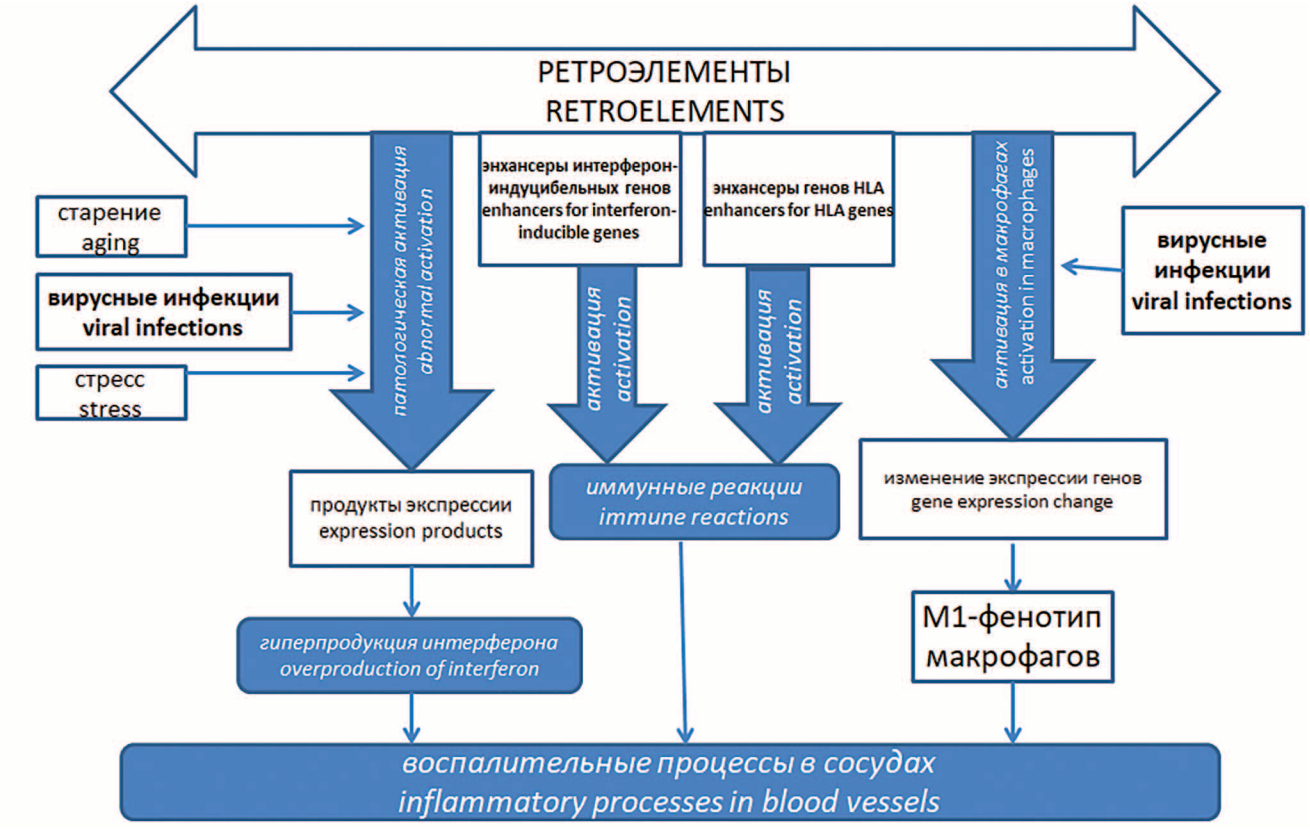

Figure 1. *Scheme of retroelements involvement in atherosclerosis development.*

C-reactive protein levels and the incidence of recurrent cardiovascular events without any impact on LDL cholesterol levels. Therefore, one promising area can be targeted change of macrophage polarisation as a result of targeting the epigenetic factors with microRNA [17]. The most optimal scheme is the use of microRNA, both for changing the macrophage polarisation and targeting abnormally active transposons.

Role of MicroRNA Derived from Retroelements in the Development of Atherosclerosis

RE involvement in aetiopathogenesis of atherosclerosis is related not only to the impact on gene expression, but also to immune system activation, however with mediation of direct formation of long ncRNA from LINE [27] and HERV transcripts [28], which have an important role to play in the development of AS [29]. Besides, microRNAs derived from retroelements [23] and involved in AS pathogenesis interact with their evolutionary sources (RE) in the genome structure and with molecules of their transcripts, leading to formation of abnormal gene networks, identification and description of which can become the basis of the efficient target therapy in AS. A potential therapeutic target can be miR-1246 originating from LTR-ERVL and partially complementary to its sequence [23]. This microRNA facilitates proliferation, invasion and differentiation of vascular smooth muscle cells (VSMC) [30]. Abnormal proliferation of VSMC causes AS plaques. VSMC can move to less differentiated forms, where VSMC markers are present, including macrophage-like cells, which facilitates progression of AS and inflammation [31].

Ageing-associated [32] miR-1248, which evolved from SINE/Alu [23], inhibits thrombomodulin expression by endothelial progenitor cells, thus evidencing its possible involvement in AS pathogenesis [33]. MiR-1257, which evolved from ERVL [23], is involved in protein assembly pathways in the major histocompatibility system (MHC) and regulates various target genes, mostly *CALR*, as well as *POMC, TLR4, IL10, ATF6*, facilitating AS progression [34]. Exosomes obtained from M2 macrophages of patients with myocardial infarction demonstrated high levels of miR-1271 [35], which evolved from LINE2 [23]. An examination of coronary artery samples of patients with AS showed a significant increase in expression of miR-1273 [36], the family of which evolved from LINE, SINE, ERVL [23].

Patients with ischemic stroke had higher levels of miR-1290 (which evolved from SINE/MIR [23]) in peripheral blood samples vs. healthy controls [37]. MiR-147, which evolved from LINE1 [23], has atherogenic effects and induces ICAM-1 (intracellular adhesion molecule 1) expression by endothelial cells (EC) [38]. During the evolution, LINE2 was a source of miR-151 [23], which inhibits EC apoptosis and plays a vital role in AS development. miR-151 targets IL-17A, BAX protein, c-caspases 3 and 9 [39]. Expression of miR-192 (which evolved from LINE2 [23]) is significantly higher in serum of patients with AS. This microRNA facilitates proliferation and migration of VSMC [40]. Serum of patients with AS demonstrates significantly reduced levels of miR-211 [41], which evolved from LINE2 [23].

Plasma samples obtained from patients with unstable angina demonstrate significantly higher levels of miR-28, which facilitates expression of ABCA1 (ATP-binding cassette subfamily, a regulator of homeostasis of cholesterol and phospholipids), which correlated with activation of LXRα translation in macrophages [42]. MiR-28 evolved from LINE2 [23] and is known for specific expression in patients with unstable angina. In this regard, miR-28 is a morphological substrate, since it is involved in pathophysiological causes of myocardial infarction. MiR-28 is located in intron 6 of *LPP* (lipoma preferable partner) and regulates migration, adhesion, proliferation, apoptosis of cells, including VSMC, in atherosclerosis [42]. High expression of miR-31 (which evolved from LINE2 [23]) facilitate AS progression as a result of effect on NOX4 (NADP oxidase-4, a non-phagocytal cell ferment which catalyses reconstruction of molecular oxygen to various active forms) [42]. Patients with chronic IHD have specifically higher expression of miR-320b, which regulates cholesterol outflow from macrophages. Administration of miR-320b to experimental animals caused atherosclerosis plaques to grow; the number of damaged macrophages increased; and pro-inflammatory cytokine levels increased due to higher phosphorylation of NF-κB [43]. During the evolution, the source of miR-320b is LINE2 [23]. Targeting miR-320b during AS therapy [43] can be a promising area, since it is the basis for resolving the issue with regulation of macrophage polarisation in a majority of current studies [17].

MiR-325, which evolved from LINE2, facilitates AS development due to inhibition of expression of *KDM1A* (which encodes lysine demethylase 1A, a component of HDAC), reducing SREBF1 (a transcription factor binding to promoter gene of low-density lipoprotein receptor) levels and inhibiting activation of PPARγ-LXR-ABCA1 pathway [44]. Plasma levels of miR-335, which evolved from SINE/MIR [23], were high in patients with AS [45]. Peripheral mononuclear cells demonstrated high levels of miR-342 [46], which evolved from SINE/tRNA-RTE [23] and positively correlated with serum concentrations of IL-6 and TNF-α [46]. Serum levels of miR-374 (which evolved from LINE2 [23] and stimulates proliferation and migration of VSMC) in patients with AS were high [47]. Reduced outflow of free cholesterol from macrophages and increased inflow of oxidised low-density lipoproteins is an important factor of AS development. MiR-378, which evolved from SINE/MIR and LINE2 [23], is involved in metabolic pathways regulating

these processes [48]. MiR-384 [49], which evolved from LINE-Dong-R4, also contributes to the development of AS due to effects on macrophages (interfering with their autophagy) [23].

Low expression of miR-421 (which originates from LINE2 [23]) in serum, plaques and VSMC in patients with IHD results in higher levels of CXCL2 (a secretory protein, which is involved in immunoregulatory and inflammatory processes) [50]. MiR-4487 (which evolved from LINE1 [23]) stimulates VSMC migration and survival and inhibits their apoptosis by targeting RASA1 (RAS suppressor, which controls cell proliferation and differentiation) [51]. Expression of miR-493 in large vessels of patients with AS is reduced as compared to controls [52]. This microRNA evolved from LINE2 [52]. MiR-495 (originating from ERVL [52]) is involved in AS pathogenesis by binding to circular RNA hsa_circ_0126672 [53]. MiR-520d (originating from SINE/Alu [23]) inhibits expression of *PCSK9* (proprotein convertase subtilisin/kexin, type 9, mutations in which cause familial hypercholesterolemia), which causes degradation of low-density lipoprotein receptors [54]. Fat tissue around coronary arteries of patients with IHD has reduced miR-548 expression. MicroRNAs in this family evolved from various REs (LINE1, LINE2, LTR-ERVL, LTR-Gypsy, LTR-ERV1, SINE/MIR) and DNA-TE (TcMar, hAT Charlie) [23]. MiR-548 regulates expression of HMGB1 (nonhistone protein binding chromatin and involved in control of DNA transcription, replication and reparation) [55]. Expression of miR-552 (which evolved from LINE1 [23]) in cerebral vessels of patients with AS increases under the influence of PDGF-BB (platelet-derived growth factor-BB) in VSMC, thus stimulating their proliferation, invasion and migration [56].

Circular RNA circ_0086296 induces AS via feedback pathway of IFIT1/STAT1, acting as a sponge for miR-576 (which evolved from LINE1 [23]). The latter inhibits expression of *IFIT1* (interferon induced protein with tetratricopeptide repeats) and prevent AS development [57]. Circular RNA has_circ_0008896 stimulates VSMC proliferation and migration by interacting with miR-633 (which evolved from SINE/MIR [23] and regulates CDC20B (cell division cycle 20B)) [58]. Expression of miR-641 (which evolved from SINE/MIR [23]) is reduced in VSMC, induced by oxidised low-density lipoproteins. This microDNA interacts with a long ncRNA MIAT, which regulates proliferation, migration and invasion of VSMC [59]. MiR-708, which evolved from LINE2 [23], is expressed in large numbers in epithelial cells of neointima in damaged vessels where the blood flow is normal. This micro RNA has anti-inflammatory effects; it inhibits expression of kinase linked to IL-1 receptor, IL-6 receptor, conserved helix-loop-helix ubiquitous kinase, inhibitor of subunit-γ of nuclear factor κB kinase [60]. Therefore, we have described 29 microRNAs which originate from RE and are involved in AS development in various ways (see Fig. 2).

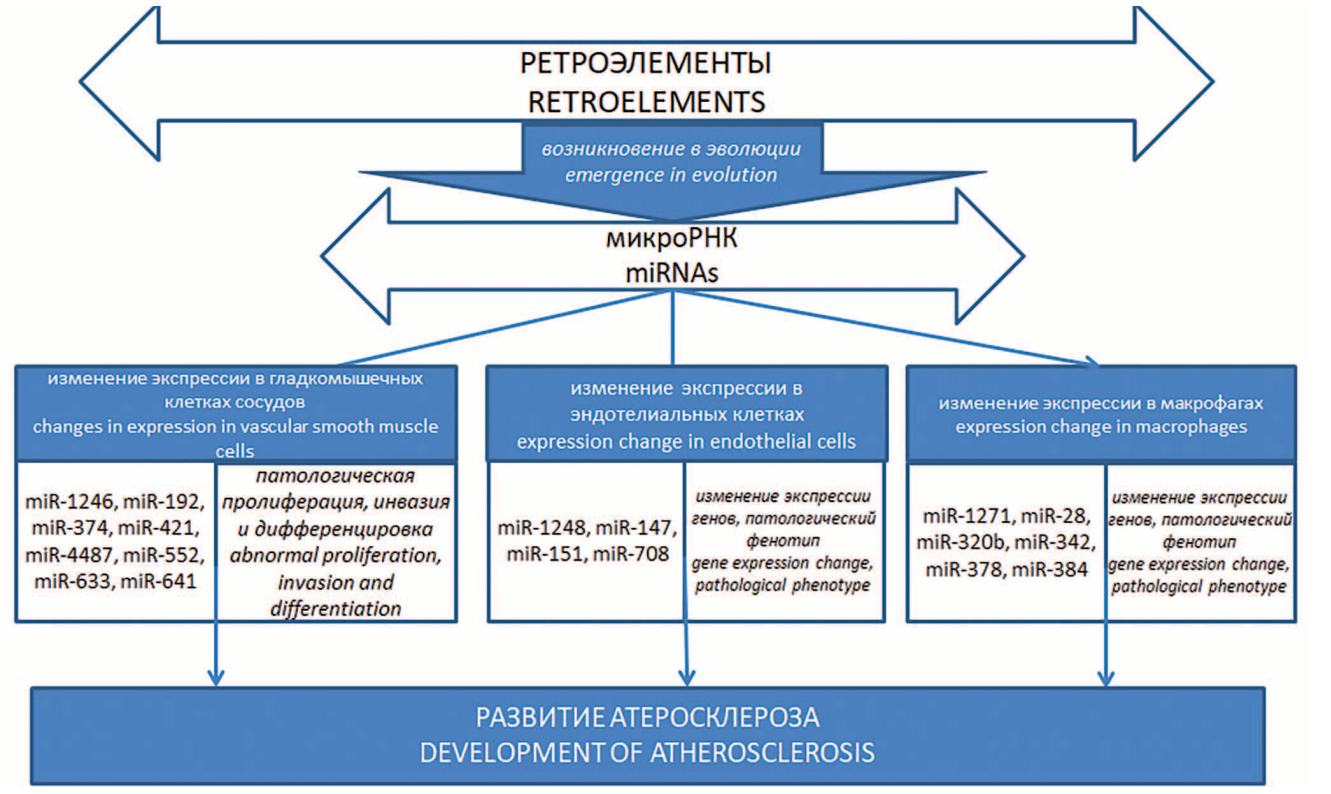

Figure 2. *Scheme of influence of microRNAs derived from retroelements in atherosclerosis development.*

Association with Ageing of MicroRNAs Originating from Retroelements, Which Are Involved in Atherosclerosis Pathogenesis

Since, during the development, REs are a source of the mentioned microRNAs, which are associated with AS, it can be assumed that one of the causes of changes in expression of these microRNAs is abnormal RE activation due to body ageing [9, 10] and resulting in chronic inflammatory processes [9, 11]. This is due to the presence of complementary RE sequences and derivative microRNAs and involvement in common epigenetic regulatory networks. In order to prove this hypothesis, scientific literature was analysed and the association between changes in the 29 microRNAs and ageing was identified. An analysis of common transcriptomic changes in microRNA with human fibroblast ageing vs. early passage cells, conducted in 2009 (Maes et al., 2009), demonstrated an association with ageing of miR-147 and miR-633 [61]. In 2010, similar works (Marasa et al., 2010) identified an increased expression of miR-1246, miR-1257, miR-1271, miR-1273, miR-548, miR-576, miR-641 [62]. In 2011, similar studies (Dhahbi et al., 2011) managed to identify changes in expression of miR-1246, miR-1290, miR-548 [63]. Serum of elderly patients (over 64 years of age) had lower miR-1248 and miR-151 concentrations as compared to a younger population [32].

A comparative analysis of extracellular vesicles showed significantly higher expression of miR-192 in old experimental animals (mice) vs. young animals. This microRNA turned out to be associated with immune processes and regulation of cytokine signalling [64]. Changes in microRNA levels in serum samples corresponded to reduced miR-211 and increased miR-374 levels in a group of people with short life expectancy vs. long-livers. MiR-211 targets mRNA of *CREB5* (encodes cAMP response element 5-binding protein), *DDIT4* (encodes DNA-damage-induced transcript 4), *IGF2R* (encodes insulin-like growth factor 2 receptor). MiR-374 targets mRNA of *ATM* (encodes serine threonine kinase ATM), *BCL2* (encodes BCL2 apoptosis regulator), *CDKN1A* (encodes cycline-dependent kinase 1A inhibitor), *CISH* (encodes cytokine-induced SH2-containing protein), *EP300* (encodes E1A-binding protein p300), *HMGB2* (encodes high mobility group box 2), *PARP1* (encodes poly(ADP-ribose) polymerase), *TP73* (encodes tumour protein p73) [65]. As far as circulating microRNAs are concerned, miR-28 [66] levels are reduced in physiologic ageing. The role of increased miR-31 expression in skin ageing has been identified, which has direct effect on mRNA of the circadian rhythm gene *Clock,* activating MAPK/ERK cascade and depleting stem cells of skin hair follicles [67]. Higher expression of miR-320b in ageing is associated with higher TNF-α levels [68]. Reduced production of miR-325 contributes to chondrocyte ageing due to activation of p53/p21 pathway [69]. MiR-335 induces EC ageing and inhibits mRNA of *sKlotho* (a protein gene product, acts as a humoral factor reducing peroxide-caused apoptosis and cellular ageing in EC) [70].

Peripheral blood mononuclears demonstrate reduced expression of miR-342 with ageing. This microRNA interacts with the coding sequence of mRNA of *SIRT6,* which facilitates ageing [71]. Computer-generated simulation aimed at decoding the impact of microRNA on skeletal muscles ageing demonstrated that miR-378 maintains stable myogenesis due to inhibition of *Msc* expression during late stages of differentiation. MiR-378 is located in the intron of *PGC-1β,* which regulates energy metabolism. MiR-378 also targets mRNA of *IGF-1* [72]. With ageing, expression of miR-384 is significantly higher in mesenchymal stem cells of the brain, which causes inhibition of osteogenetic differentiation, thus contributing to ageing. MiR-384 inhibits mRNA of *Gli2* (encodes the protein of zinc finger family GLI2) [73]. In ageing, expression of miR-421 in the anterior lens capsule is significantly reduced, which facilitates cataract development. MiR-421 is an apoptosis inhibitor and induces cell proliferation [74]. A study of skin samples taken from people of various ages demonstrated that increased expression of miR-4487, which interacts with circular RNAs, has a role to play in skin ageing [75]. The role of reduced miR-493 expression in myocardium ageing has been established [76].

Higher miR-495 expression contributes to cell apoptosis and ageing of mesenchymal stem cells by impacting *BM1* (encodes proto-oncogene BMI1) [77]. It has been established that miR-520d reduces expression of the long ncRNA GPRC5D-AS1, which inhibits cell apoptosis and activates factors of muscle regulation Mef2c, Myf5, MyoD, Myo G. MiR-520d facilitates skeletal muscles ageing [78]. One sign of skin ageing is impaired calcium gradient. Higher calcium concentrations in the basal layer inhibit cell proliferation, while reduced concentrations in the granular layer change the keratinised layer composition. Keratinocytes respond to calcium-induced blocking of mitosis with higher expression of specific microRNAs, including miR-552 [79]. With ageing, expression of miR-708 in joint tissue and serum drops [80]. Table 1 presents data on the changes in expression of the 29 microRNAs originating from RE, in ageing and atherosclerosis. The results allow assuming that, with ageing, RE activation leads to immunopathological processes and disorders in epigenetic networks for gene regulation, resulting in modified expression of specific microRNAs (which evolved from REs and have complimentary sequences), which contribute to AS development.

According to a systematic review of scientific literature conducted in 2023, both experimental and clinical trials are ongoing which seek to explore the direct impact on epigenetic factors of atherosclerosis. The role of

Table 1. *Association of retroelement-derived miRNAs with atherosclerosis and aging*

№	MiRNA	Retroelement-source	Changes in miRNAs expression in atherosclerosis (increase — ↑, decrease — ↓) [author]	Changes in miRNAs expression during aging (increase — ↑, decrease — ↓) [author]
1.	miR-1246	ERVL	↑ [30]	↑ [62, 63]
2.	miR-1248	SINE/Alu	↑ [33]	↓ [32]
3.	miR-1257	ERVL	↑ [34]	↓ [62]
4.	miR-1271	LINE2	↑ [35]	↑ [62]
5.	miR-1273	LINE, SINE, ERVL	↑ [36]	↑ [62]
6.	miR-1290	SINE/MIR	↑ [37]	↑ [63]
7.	miR-147	LINE1	↑ [38]	↓ [61]
8.	miR-151	LINE2	↓ [39]	↓ [32]
9.	miR-192	LINE2	↑ [40]	↑ [64]
10.	miR-211	LINE2	↓ [41]	↓ [65]
11.	miR-28	LINE2	↑ [42]	↓ [66]
12.	miR-320b	LINE2	↑ [43]	↑ [68]
13.	miR-325	LINE2	↑ [44]	↓ [69]
14.	miR-335	SINE/MIR	↑ [45]	↑ [70]
15.	miR-342	SINE/tRNA-RTE	↓ [46]	↓ [71]
16.	miR-374	LINE2	↑ [47]	↑ [65]
17.	miR-378	SINE/MIR, LINE2	↑ [48]	↓ [72]
18.	miR-384	LINE-Dong-R4	↑ [49]	↑ [73]
19.	miR-421	LINE2	↓ [50]	↓ [74]
20.	miR-4487	LINE1	↑ [51]	↑ [75]
21.	miR-493	LINE2	↓ [52]	↓ [76]
22.	miR-495	ERVL	↓ [53]	↑ [77]
23.	miR-520d	SINE/Alu	↓ [54]	↑ [78]
24.	miR-548	LINE, ERV, SINE	↓ [55]	↓ [62, 63]
25.	miR-552	LINE1	↑ [56]	↑ [79]
26.	miR-576	LINE1	↓ [57]	↓ [62]
27.	miR-633	SINE/MIR	↓ [58]	↑ [61]
28.	miR-641	SINE/MIR	↓ [59]	↑ [62]
29.	miR-708	LINE2	↓ [60]	↓ [80]

medicinal products in the mechanisms of the disease is being studied as well. For example, clinical trials demonstrated that aspirin absorption results in reduced methylation of *ABCB1* (encodes a member of ATP-binding cassette subfamily) in patients with stenotic intracraneal arteries. The role of plant mixes used in China, as well as of curcumin, resveratrol and geniposide on DNA methylation in AS was established. The efficacy of DNA methyltransferases (DNA-MT) inhibitors [81] (which are actively used in the treatment of malignancies [82]) for the treatment of AS was demonstrated. In mice experiments, an analogue of cytosine (5-azacytidine) inhibited AS development. Antisense oligonucleotides, e.g. MG98, can be successfully used as DNA-MT inhibitors for the treatment of AS. Epigenetic therapy can target histone modification enzymes; histone methyltransferase inhibitors (iHMT) and histone acetyltransferase inhibitors (iHAT) can be used. Currently, iHMTs are an unemployed resource, the most potent of them being GSK126, a highly-selective component to methyltransferase EZH2, which can inhibit expression of pro-inflammatory genes. Anacardic acid and garcinol are natural iHATs. MG149, a synthetic analogue of anacardic acid, inhibits NF-κB pathway, which contributes to AS development. A promising class of products is histone deacetylase inhibitors (iHDA), because they have already been approved by the FDA for the treatment of haematologic cancers and can re-activate silent genes by targeted impact on target gene

promoters. In mice experiments, the most promising iHDA was Vorinostat (approved for T-cell lymphoma) [81]. In addition to the described impact of plant mixes and known medicinal products on epigenetic changes in AS, an experiment on 36 male C57BL/6J mice with zero ApoE aged 10 weeks demonstrated an effect from exercises on microRNA expression: reduced miR-155 levels and increased miR-126, miR-146a levels. Mice were placed in a chamber with a run track 10 minutes before the running started. The pace was 13 m/min for 60 minutes daily from 06.00 pm to 07.00 pm, with a zero percent slope. These mice demonstrated higher expression of miR-126 and miR-146a, which facilitated reduction in inflammatory vascular damage by inhibition of TRAF and TLR4 signalling, vs. controls (statins and no treatment) [83].

The problem of epigenetic therapy is its low bioavailability and side effects, because target molecules are expressed in tissues all over the body. Therefore, nanomaterials are used to ensure targeted exposure of atherosclerotic foci in vessels. For this purpose, specific liposomes, micelles and nanoparticles of high-density lipoproteins are used [81]. The use of biologically mineralised, framed nanoparticles with a neutrophil membrane coating, containing anti-miR-155, has been described, which ensured inhibition of miR-155 expression in the endothelial wall of vessels, thus preserving translation of *BCL6* [84]. Currently, new drugs from the group of a modified double-stranded short interfering RNA have been registered and are used, e.g. Inclisiran, which inhibits translation of proprotein convertase subtilisin/kexin, type 9 (*PCSK9*), in liver and ensures stable reduction in LDL cholesterol. Phase 3 randomised, placebo-controlled clinical trials in 3,660 subjects demonstrated that, when Inclisiran is prescribed twice a year with or without the maximum tolerated statin dose, this drug is efficient, safe and well-tolerated in lowering LDL cholesterol levels in adult patients with heterozygous familial hypercholesterolemia and AS [85]. Another short interfering RNA, Olpasiran, inhibits expression of *LPA* at the mRNA level. Since plasma concentrations of apolipoprotein (a component of LDL), encoded by *LPA,* positively correlate with the risk of AS, Olpasiran is used in the therapy of AS. Olpasiran enters the liver via N-acetylgalactosamine fragment, which binds to apolipoprotein receptor on the liver surface. In hepatic cells, this short interfering RNA binds to mRNA of *LPA* with the help of an RNA-induced silencing complex (RISC) due to nucleotide sequence complementariness. A multicenter randomised, placebo-controlled trial OCEAN(a)-DOSE in patients with atherosclerosis and high apolipoprotein levels after Olpasiran therapy for 48 weeks (SC injections of the drug once every 12 weeks) demonstrated efficacy and safety vs. placebo [86]. The search for new drugs, where the main component is non-coding RNA, is ongoing. New potential RNA-targeting agents for reliable reduction of apolipoprotein levels are drugs encoded like SLN360 and LY3819469 (Lepodisiran), which are also short interfering RNAs targeting post-transcriptional inhibition of mRNA of *LPA* [87]. The microDNAs, described in this article and originating from RE, can also be the basis for inhibition of transposons, activated in atherosclerosis, which is one of the methods to overcome side effects caused by non-specific exposure to epigenetic therapy in AS.

Conclusion

Analysis of scientific literature allowed to conclude that the key role in AS initiation and development is played by ageing-mediated excessive activation of REs, which causes interferon stimulation and immunopathological processes. Viral infections and stress are also of importance; they activate RE to protect cells, which can be a cause of early onset and progression of AS. Since statins and aspirin used in the therapy of AS do not affect specifically macrophages and their polarisation and do not impact disease progression, new ways to affect AS should be searched for. There were attempts to use monoclonal antibodies to chemokines and cytokines, antagonists of chemokine receptors and adhesion molecules, matrix metalloproteinase inhibitors in the therapy of AS. However, these methods did not demonstrate any significant effect. The most promising area is epigenetic exposure of the genes involved in AS pathogenesis, *PCSK9* (Inclisiran) and *LPA* (Olpasiran), to short interfering RNAs, which demonstrated significant effect in clinical trials. Therefore, targets for epigenetic exposure in AS should be searched for; these can be REs. Their ageing-mediated excessive activation results in interferon stimulation and immunopathological processes. Since REs are a source of long ncRNAs and microRNAs, their impaired expression in AS reflects RE dysregulation. Thus, a promising therapy for this disease can be target therapy with specific microRNAs, directed against pathologically activated REs involved in AS pathogenesis. The 29 RE-originating microRNAs described in this study, which are associated both with ageing and AS, can be used as tools for epigenetic target therapy. These microRNAs are involved not only in immune reactions, but they also impact expression of various genes in VSMC, EC and macrophages, thus demonstrating complex mechanisms of AS development with involvement of various signalling pathways in specific cell types.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2024-14-2-96-107
УДК 616.361-002-004-021.3-036-079.4-085
EDN: FGADIS

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ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ, ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ И ЛЕЧЕНИЯ IgG_4-СКЛЕРОЗИРУЮЩЕГО ХОЛАНГИТА

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Clinical Features, Differential Diagnosis and Treatment of IgG_4-Related Sclerosing Cholangitis

Резюме

Цель обзора: представить современный взгляд на особенности клинического течения, дифференциальной диагностики и лечения IgG_4-склерозирующего холангита. **Основные положения**. IgG_4-склерозирующих холангит — фиброзно-воспалительное заболевание, при котором поражаются внутрипеченочные и внепеченочные желчные протоки. Проявления IgG_4-склерозирующего холангита схожи с изменениями при первичном склерозирующем холангите, опухолях желчных протоков и поджелудочной железы, в связи с чем, более трети пациентов с IgG_4-склерозирующим холангитом подвергаются оперативным вмешательствам. На данный момент отсутствуют специфичные и чувствительные методы диагностики данного заболевания. Повышение уровня сывороточного IgG_4 наблюдается при многих других заболеваниях. Четырёхкратное повышение IgG_4 в сыворотке крови является более надежным маркером для диагностики IgG_4-склерозирующего холангита, однако такое значение наблюдается лишь у небольшой доли пациентов. При визуализации желчных протоков выявляются сегментарные или протяженные стриктуры с престенотическим расширением и утолщением стенок. Глюкокортикостероиды остаются первой линией терапии для индукции и поддержания ремиссии заболевания. Рецидив наблюдается более чем у половины пациентов. Некоторые исследования также указывают на повышенный риск развития злокачественных опухолей. В данном обзоре освещены клинические и лабораторно-инструментальные проявления IgG_4-склерозирующего холангита, проведена сравнительная характеристика с первичным склерозирующим холангитом и холангиокарциномой, а также представлены возможности терапии, прогноз и исходы заболевания. **Заключение.** IgG_4-склерозирующий холангит — редкое и сложно диагностируемое заболевание, требующее проведения тщательной дифференциальной диагностики с первичным склерозирующим холангитом, раком желчных протоков и поджелудочной железы. Несмотря на относительно благоприятное течение и эффективность глюкокортикостероидов, заболевание часто рецидивирует и имеет неизвестный долгосрочный прогноз. Особое внимание уделяется риску развития злокачественных новообразований у данной группы пациентов, что подчеркивает необходимость пожизненного наблюдения за пациентами.

Ключевые слова: *IgG_4-склерозирующий холангит, первичный склерозирующий холангит, холангиокарцинома, иммуноглобулин IgG_4, аутоиммунный панкреатит*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 06.02.2024 г.

Принята к публикации 12.03.2024 г.

Для цитирования: Гусева А.К., Охлобыстин А.В. ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ, ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ И ЛЕЧЕНИЯ IgG_4-СКЛЕРОЗИРУЮЩЕГО ХОЛАНГИТА. Архивъ внутренней медицины. 2024; 14(2): 96-107. DOI: 10.20514/2226-6704-2024-14-2-96-107. EDN: FGADIS

Abstract

The aim: To present the state-of-the-art of clinical features, differential diagnosis and treatment of IgG_4-related sclerosing cholangitis. **Key points:** IgG_4-sclerosing cholangitis is a fibrotic inflammatory disease affecting the intrahepatic and extrahepatic bile ducts. The clinical features of IgG_4-sclerosing cholangitis are similar to those of primary sclerosing cholangitis, bile duct cancer and pancreatic cancer. More than one third of patients with IgG_4-sclerosing cholangitis undergo surgery. Currently, there are no specific and sensitive methods to diagnose this disease. Increased serum IgG_4 levels are observed in many other diseases. A fourfold increase in serum IgG_4 levels is a more reliable marker, but this feature is found in only a small percentage of patients. The imaging of bile ducts usually reveals segmental or extended strictures with prestenotic dilatation and wall thickening. Glucocorticosteroids are the first-line therapy for induction and maintenance of disease remission. More than a half of patients develop relapses. Several studies have found an increased risk of malignant tumors. This review describes the clinical, laboratory, and instrumental features of IgG_4-sclerosing cholangitis. Comparative evaluation of diseases manifestations versus primary sclerosing cholangitis and cholangiocarcinoma is presented along with options of therapy, prognosis and outcomes of the disease. **Conclusion:** IgG_4-sclerosing cholangitis is a rare and difficult to diagnose disease that requires careful differential diagnosis with primary sclerosing cholangitis, bile duct cancer and pancreatic cancer. Despite its relatively benign course and efficacy of glucocorticosteroid therapy, the disease recurs frequently and has an unknown long-term outcome. Special attention is paid to the risk of malignant neoplasms in this group of patients, emphasizing the need for lifelong follow-up.

Key words: *IgG_4-related sclerosing cholangitis, primary sclerosing cholangitis, cholangiocarcinoma, immunoglobulin IgG_4, autoimmune pancreatitis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 06.02.2024

Accepted for publication on 12.03.2024

For citation: Guseva A.K., Okhlobystin A.V. Clinical Features, Differential Diagnosis and Treatment of IgG_4-Related Sclerosing Cholangitis. The Russian Archives of Internal Medicine. 2024; 14(2): 96-107. DOI: 10.20514/2226-6704-2024-14-2-96-107. EDN: FGADIS

AIP — autoimmune pancreatitis, GCS — glucocorticosteroids, MNP — malignant neoplasms, CT — computer tomography, MRI — magnetic resonance imaging, PSC — primary sclerosing cholangitis, US examination — ultrasound examination, CC — cholangiocarcinoma, AMA — anti-mitochondrial antibodies, ANA — anti-nuclear antibodies, ANCA — antineutrophil cytoplasmic antibodies, ASMA — anti-smooth muscle antibody, HLA — human leukocyte antigen, IgG_1 — immunoglobulin G_1, IgG_2 — immunoglobulin G_2, IgG_4 — immunoglobulin G_4, IgG_4-AD, immunoglobulin G_4-associated disease, IgG_4-SC — immunoglobulin G_4– associated sclerosing cholangitis, SIR — standardised incidence ratio

Introduction

Immunoglobulin G_4-associated sclerosing cholangitis (IgG_4-SC) is a biliary manifestation of systemic IgG_4-associated disease (IgG_4-AD) [1, 2]. IgG_4-SC manifests as diffuse or focal inflammatory infiltration with IgG_4-positive plasma cells of intrahepatic and extrahepatic bile ducts, development of moire fibrosis, often with type 1 autoimmune pancreatitis, and rapid response to glucocorticosteroid therapy [3]. Due to similar clinical and instrumental manifestations of this condition and primary sclerosing cholangitis (PCS), bile duct and pancreatic cancer, over a third of patients undergo various surgeries [4]. The outcome and prognosis of this disease are understudied; however, more and more information suggests a higher risk of malignant neoplasms (MNOs) in patients with IgG_4-SC [1, 5, 6]. Glucocorticosteroids (GCS) are used as an induction and maintenance therapy for disease remission [3]. Nevertheless, according to various studies, 30–50 % of patients experience relapses within 6 months after glucocorticosteroid discontinuation[7, 8]. This review presents current information on clinical course, differential diagnosis and therapy of IgG_4-associated sclerosing cholangitis.

Epidemiology

According to the literature, the incidence of IgG_4-SC is 2 cases per 100,000 people [9]. IgG_4-SC affects primarily men (the ratio of 4 : 1) over 60 years of age (median age: 66.2 years old) [10, 11]. However, according to the studies, where the condition was observed in patients of 23 to 83 years of age, it can affect younger patients [7, 11].

Aetiology and Pathogenesis

Aetiology and pathogenesis of IgG_4-SC are understudied [12]. The impact of genetic factors has been discussed, e.g. a genome-wide association study (GWAS), which enrolled 835 patients from Japan with various variants of IgG_4-AD, established that genes HLA-DRB1 and FCGR2B are associated with a higher risk of IgG_4-AD [13]. A majority of studies conclude that an autoimmune inflammation has a role to play in the disease pathogenesis. Patients with IgG_4-SC had antibodies to galectin-3, laminin 511-E8, prohibitin 1, and annexin A11 [14–17]. However, no specific autoantibodies have been found. There is an evidence of a possible contribution by allergic mechanisms in IgG_4-AD. Increased serum IgE levels are observed in 30 % of patients with type 1 autoimmune pancreatitis (AIP), and every fifth patient has a history of allergic diseases, such as bronchial asthma, drug-induced allergy or chronic rhinosinusitis [17]. The possible role of changed microbiota in IgG_4-SC development has been studied. An examination of faeces of patients with PSC, IgG_4-SC and controls demonstrated reduced alpha diversity and changes in microbiota composition in the study groups vs. controls [18]. Besides, significant

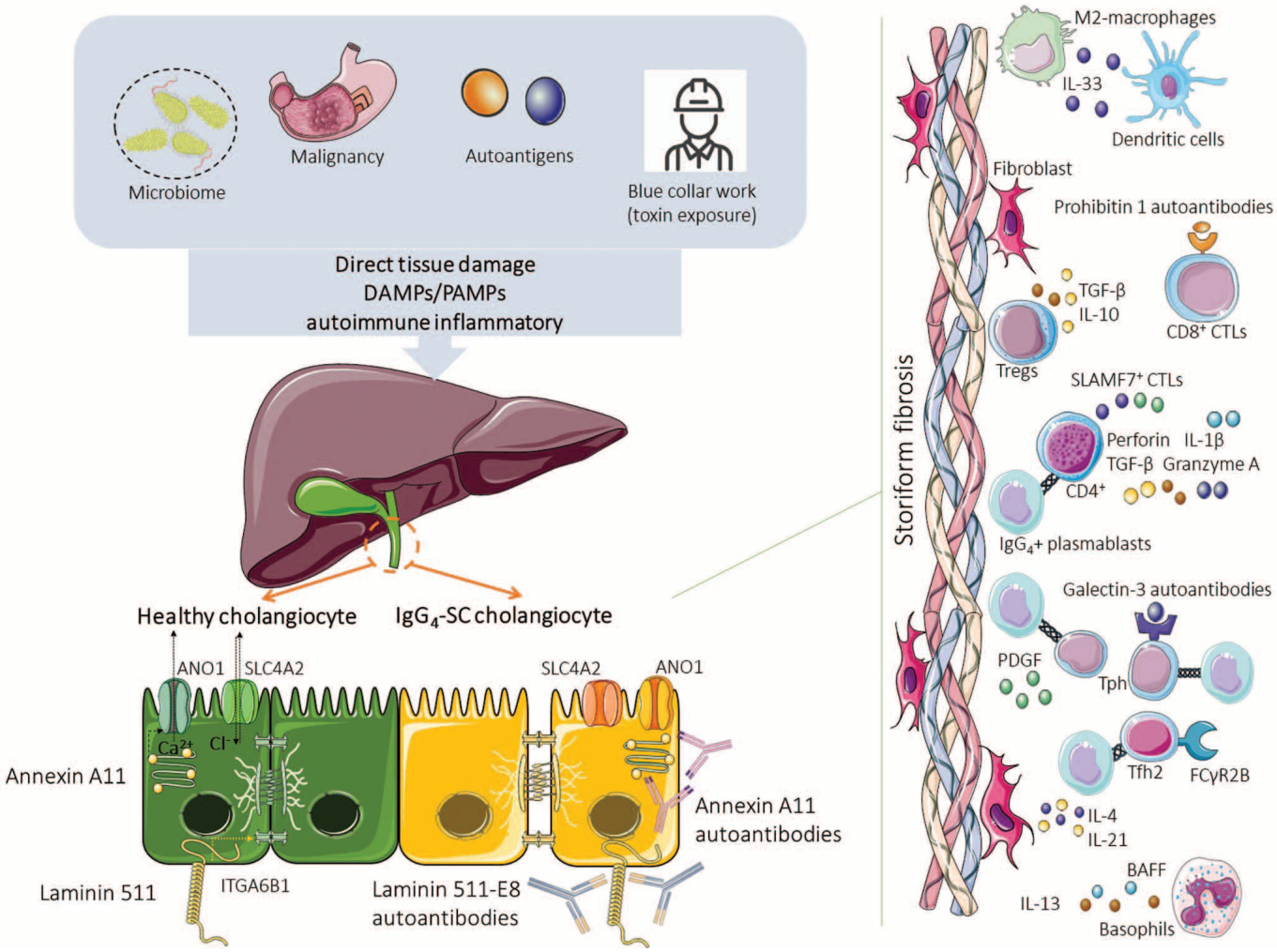

Figure 1. *Proposed pathogenesis of IgG_4-related sclerosing cholangitis*

Note: Exposure to autoantigens, DAMPs/PAMPs (produced by altered microbiome/malignant tumors) and hazardous industrial factors, through molecular mechanisms of mimicry, are possible causes of IgG_4-CX development. Activation of the innate immune system leads to disruption of the adaptive immune system. IgG_1 and IgG_4 plasmablasts produce autoantibodies against annexin A11, laminin 511-E8, galectin-3, and progibitin 1. Antibodies against annexin A11 disrupt Cl^- and Ca^{2+} transport via ANO1 to the apical membrane of cholangiocytes. Antibodies against laminin 511-E8 block binding to membrane receptors (ITGA6B1), impairing cholangiocellular barrier function. Antibodies to galectin-3 and progibitin-1 affect B- and T-cell activation. Oligoclonal IgG_4 plasmoblasts support immune dysregulation through stimulation and reactivation of oligoclonal CD4 SLAMF7 cytotoxic T cells. In addition, due to PDGF secretion they contribute to the formation of storiform fibrosis.

Abbreviations: ANO1 — anoctamin 1; **BAFF** — B-cell activation factor; **CD4** — cluster of differentiation 4; **CTLs** — cytotoxic T lymphocytes; **DAMPs** — damage-associated molecular patterns; **PAMPs** — pathogen-associated molecular patterns; **FCγR2B** — Fc γ receptor 2B; **ITGA6B1 —** integrin α6β1; **SLAMF7** — signaling lymphocytic activation molecule family member 7; **PDGF —** platelet-derived growth factor; **SLC4A2 —** solute carrier family 4 member 2; **Tfh** — follicular T helper 2 cells; **TGF-β** — Transforming growth factor-β; **Tph** — peripheral T helper cells; **Tregs —** regulatory T cells.

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differences in microbiota composition in patients with PSC and IgG_4-SC [21] have been noted. The study of unfavourable environmental factors is also of great importance. A study of 101 patients with IgG_4-SC and autoimmune pancreatitis (AIP) showed that 68 % of them were blue-collar-workers, i.e. those who were manual industrial labourers exposed to industrial solvents and gases [19]. This value was far higher than in controls, where blue-collar-workers accounted for 39 % (OR = 3.66; 95 % CI: 2.18–6.13; n = 404; $p < 0.0001$). Moreover, it has been found out that prolonged contact with industrial gases, dust and organic substances, such as asbestos, for over a year is associated with a higher risk of IgG_4-SC and AIP (OR = 2.14; 95 % CI: 1.26–3.16; $p < 0.001$, and OR = 2.95; 95 % CI: 1.78–4.90; $p < 0.001$, respectively) [19]. Figure 1 shows key concepts of possible pathogenesis of IgG_4-SC.

Clinical Presentation

Approximately 25 % of IgG_4-SC cases are asymptomatic [11]. Most common manifestations of IgG_4-SC are obstructive jaundice (35–80 %), sharp weight loss, moderate abdominal pain, rarely — skin itching (13 %) [11]. Often, patients who underwent bile duct treatment and diagnostic procedures experienced signs of infectious cholangitis, such as fever [20]. According to various sources, 72–95 % of IgG_4-SC patients had concomitant type 1 AIP [11, 21, 22]. Such cases presented with manifestations associated with the development of exocrine and endocrine deficiency of pancreas (53 % and 37 %, respectively) [7]. Also, in numerous cases, IgG_4-SC was concomitant to other IgG_4-associated diseases, such as tubulo-interstitial nephritis (5 %), dacryoadenitis (15 %), salivary adenitis (26 %), retroperitoneal fibrosis (5 %), mediastinal and axillary lymphoadenopathy (8 %) [10].

Laboratory Diagnostics

Blood samples of patients with IgG_4-SC demonstrate higher cholestasis marker levels: alkaline phosphatase, gamma-glutamyltranspeptidase, total bilirubin, mainly due to direct fraction [3, 23]. Increased serum IgG_4 levels of > 1.35 g/L were observed in 75–90 % of patients with IgG_4-SC [22, 24, 25]. Studies showed that a 4-fold increase in blood IgG_4 levels was highly specific and had positive prognostic value (100 %); however, sensitivity was significantly reduced and made 42 % (95 % CI: 31–55) [3, 24, 26]. Also, there are cases of moderately increased serum IgG_4 levels in patients with PSC (9–22 %) and cholangiocarcinoma (CC) (8–14 %)[22, 27, 28]. Table 1 shows average serum IgG_4 levels in IgG_4-SC and other diseases. According to a Japanese study, the threshold value of serum IgG_4 of 2.07 g/L can be a useful additional tool to differentiate types 3 and 4 IgG_4-SC and CC [22]. In order to differentiate IgG_4-SC and PSC, the threshold value of serum IgG_4 was 1.77 g/L, with the sensitivity and specificity being 91.5 % and 87.6 %, respectively [22]. A study

Table 1. *Mean serum IgG_4 levels in IgG_4-sclerosing cholangitis, primary sclerosing cholangitis, cholangiocarcinoma and pancreatic cancer*

Disease	Serum IgG_4 (M±SD)			
	Hirano et al. 2006[33]	Ohara et al. 2013 [22]	Nakazawa et al. 2012[34]	Oseini et al. 2011[35]
IgG_4-SC	-	6,46±6,62	-	2,771±0,552**
IgG_4-SC type 1 vs PCa	-	6,13±6,18* **vs** 0,593±0,659*	5,48±7,71* **vs** 0,49±0,73*	-
IgG_4-SC type 2 vs PSC	-	7,99±8* **vs** 0,687±0,86*	8,84±8,54* **vs** 0,5±0,45*	-
IgG_4-SC types 3,4 vs CC	-	6,46±7,11* **vs** 0,523±0,468*	5,14±5,42* **vs** 0,64±0,59*	-
PSC	1,86±2,41	-	-	-
CC	0,624±0,378	-	-	0,646±0,063**
PCa	66±3,8	-	-	-

Note: IgG_4-SC — IgG_4-sclerosing cholangitis; PSC — primary sclerosing cholangitis; CC — cholangiocarcinoma; PCa — pancreatic cancer.
* $p < 0.05$
**M±SEM

by Boonstra K. et al. established that, if IgG_4 levels are up to two normal values, it is recommended to measure the IgG_4/IgG_1 ratio, which in IgG_4-SC was ≥ 0.24, with the sensitivity and specificity being 86 % and 95 %, respectively [26]. Similar results were obtained by Liming Tan et al. (2019), who analysed blood levels of IgG_4, CA19-9, autoantibodies (ANA, ASMA, AMA, ANCA) in 45 patients with IgG_4-SC, 80 — with PSC, 41 — with biliary duct tumour, 52 — with pancreatic cancer, and 48 healthy volunteers [29]. The study demonstrated that a higher serum IgG_4 level was observed in patients with IgG_4-SC (86.67 %) vs. controls ($p < 0.01$) [29]. Serum IgG_4 levels were also elevated in patients with PSC (25 %), bile duct cancer (7.32 %) and pancreatic cancer (9.62 %) [29]. Positive ANAs were observed in patients with IgG_4-SC and PSC (40 % and 32.5 %, respectively); however, the difference was not statistically significant [29]. The rate of ANCA, ASMA and AMA in patients with IgG_4-SC was significantly lower than in patients with PSC ($p < 0.01$) [29]. Positive ANCAs were observed more often in patients with PCS as compared to patients with IgG_4-SC (61.25 % and 6.67 %, respectively) ($p < 0.01$)[29]. CA19-9 levels were higher in over a half of patients with IgG_4-SC (51.11 %) and in a majority of patients with bile duct adenocarcinoma and pancreatic cancer (92.68 % and 90.38 %, respectively) [29]. Significant changes in CA19-9 levels reduced in the presence of jaundice. Also, there are published data on increased bile IgG_4 levels in patients with IgG_4-SC. The threshold value of 0.038 g/L allowed differentiating IgG_4-SC and patients with PSC and CC, with sensitivity and specificity being 100 % and 77 %, respectively [30]. However, in order to implement this method in the wide clinical practice, additional studies are required. Patients with IgG_4-SC and AIP had higher IgG_2 values as compared to patients with isolated autoimmune pancreatitis or primary sclerosing cholangitis, with high specificity (97 %) and positive prognostic value (91 %) [38]. High IgG_1 levels (8.2 ± 2.6 g/L) indicated primary sclerosing cholangitis [31]. Also, it has been established that the IgG_4/IgG ratio of > 0.129 was more often indicative of IgG_4-AD (OR 31.25; 95 % CI: 15.31–63.79; $p < 0.001$) [32].

Classification

In 2004, Nakazawa et al. proposed an IgG_4-SC classification taking into account the cholengiography pattern [36]. ***Type 1*** (64 %) is associated with narrowing of the distal section of the choledochous duct. Isolation of this type is disputable, because some experts believe that duct narrowing is a result of compression of an enlarged pancreatic head [37]. However, is some cases, type 1 IgG_4-SC is not associated with autoimmune pancreatitis [38]. This type should be differentiated from pancreatic head tumour, pancreatic pseudotumor and cholangiocarcinoma. ***Type 2*** is characterised by involvement of intrahepatic and extrahepatic bile ducts. This type is further subdivided into type 2a (5 %) and type 2b (8 %). Type 2a presents with narrowing of intrahepatic bile ducts and prestenotic enlargement. In type 2b, narrowing of intrahepatic bile ducts is combined with reduction in the number of side ducts, however, without prestenotic enlargement. In this type, differential diagnosis is with PSC. ***Type 3*** of IgG_4-SC (10 %) is characterised by narrowing of the distal section of the choledochous duct and confluence area. ***Type 4*** (10 %) manifests only with duct narrowing near the hepatic hilum. Types 3 and 4 of IgG_4-SC mimic changes typical of CC, therefore, morphological verification is essential in order to rule out tumour. If changes on a cholangiogram do not correspond to any of these types, the condition should be classified as an unidentified type. Comparison of IgG_4-sclerosing cholangitis, primary sclerosing cholangitis and cholangiocarcinoma is presented in Table 2.

Methods of Instrumental Diagnostics

Images of bile ducts in IgG_4-SC patients demonstrate segmental or extensive stenosis of bile ducts, with prestenotic enlargement and wall thickening [49]. PSC is characterised by short, moniliform stenosis, with diverticula-like duct protrusion [36]. According to another study, typical signs of IgG_4-sclerosing cholangitis seen during intraduct ultrasound were circular symmetric thickening of bile duct wall with even external and internal edges, as well as wall thickening up to > 0.8 mm outside the stenosis area [50]. This threshold wall thickness was highly sensitive (95–100 %) and specific (91 %) for differentiation from CC [50]. Comparison of changes seen during intraduct ultrasound is presented in Table 3. According to studies, CT signs of IgG_4-SC include: circular duct wall thickening with an even external and internal contour; uniform contrast accumulation in arterial phase; involvement of the intrapancreatic section of the bile duct; discontinuity of involvement; concomitant changes in pancreas; visible lumen; funnel-like narrowing of the proximal section of the common bile duct; extended bile ducts proximal to stenosis to 9 mm [51]. A comparative study by Yata

Table 2. *Comparative characterization of IgG_4-sclerosing cholangitis, primary sclerosing cholangitis and cholangiocarcinoma*

Parameter	IgG_4-SC	PSC	CC
Prevalence	2/100.000[9]	1-16/100.000[39]	5,9/100.000[40]
Age (years)	50–60[24]	25–45[41]	50–70[42]
Gender (m:f)	4–8:1[23]	2:1[43]	1.5:1[44]
Clinical features	jaundice, significant weight loss, epigastric pain [24]	up to 50 % asymptomatic, jaundice, pruritus [45]	asymptomatic in early stages, especially in intrahepatic CC; painless jaundice in 90 % of patients with extrahepatic CC [46]
Other organ involvement	type 1 AIP (up to 90 %), generalized lymphadenopathy, sialoadenitis, retroperitoneal fibrosis [24]	50–80 % IBD [45] (85–90 % — UC; 10–15 % -CD)	metastases
Elevated serum IgG_4 level	74–90 %[26]	9–22 %[27]	8–22 %[22,28]
CA-19-9	51 % 153–292 U/ml[29]	12 % 47–97 U/ml[29]	93 % 329–384 U/ml[29]
pANCA	7 %[29]	61 %[29]	-
Histology	lymphoplasmacellular infiltrate (>10 IgG_4+ plasma cell, IgG_4/IgG>0,40), storiform fibrosis, obliterative phlebitis[47]	periportal sclerosis, onion-skin fibrosis[47]	dysplasia, biliary neoplasia, atypical cells[47]
Immunohistochemistry: IgG_4+ plasma cell	50–90 %[24]	5–25 %[27]	25 % (n=4)[48]
Immunohistochemistry: IgG_4+:IgG+ plasma cell ratio	>0.40[24]	-	-
Response to GS	rapid, distinct in the early stages[3,23]	no[39]	-
Prognosis	favorable[23,24]	progressive disease, depends on the response to UDCA [41]	at 5 years after diagnosis, survival rates range from 7 % to 20 %[40]

Note: IgG_4-SC — IgG_4-sclerosing cholangitis; PSC — primary sclerosing cholangitis; CC — cholangiocarcinoma; GS — glucocorticoids; UDCA — ursodeoxycholic acid

M. et al. (2016) demonstrated that a combination of the above CT signs was sensitive (80 %) and specific for differentiation from CC [51]. Besides, a double contour see on CT was highly specific for cholangiocarcinoma (90 %), unlike single-layer contrast accumulation in IgG_4-SC [51]. Tokala A. et al. (2014) proposed to use the wall thickness of the common bile duct of > 2.5 mm, seen on MRI, as a diagnostic criterion to differentiate from PSC [49]. In 71.4–100 % of cases, thickened bile duct walls evenly accumulated contrast [49, 52, 53], and were iso- or hyperintense during the portal vein or delayed phase vs. hepatic parenchyma [49, 52, 53].

Morphological Characteristics

Typical morphological changes in IgG_4-SC are lymphoplasmacytic infiltration, moire fibrosis, obliterating phlebitis, sometimes — eosinophilic infiltration [3]. In order to verify IgG_4-SC morphologically, it is required to observe at least 10 IgG_4-positive plasma cell HPF (x400) in the fine-needle aspiration material, or > 50 cells in intraoperative samples, including edge biopsy, and the ratio of IgG_4/IgG-positive cells of at least 40 % [20, 55]. However, IgG_4-positive plasma cells can be observed in PSC and cholangiocarcinoma [9, 28]. Typical morphological changes in IgG_4-SC were usually absent, since the key changes take place in submucosa and deeper [9].Moreover, stenting can cause non-specific changes, such as atypical epithelial cells, epithelial ulceration and inflammatory infiltration, which can facilitate incorrect interpretation as signs of PSC and CC [56, 57]. In fine-needle biopsy of the liver, only 57 % of patients with intrahepatic involvement of hepatic ducts had > 10 IgG_4-positive plasma cells and only in 8 % of cases — with involvement of extrahepatic bile ducts only [58]. Sensitivity and specificity of intraductal biopsy were 52 % and 96 %, respectively [59]. Biopsy of major duodenal papilla ampulla is indicated

Table 3. Comparative characterization of intraductal ultrasound findings in patients with IgG_4-sclerosing cholangitis, primary sclerosing cholangitis and cholangiocarcinoma

Parameter	Naitoh I., et al., 2009[50]			Kubota K., et al., 2011[6]			Naitoh I., et al., 2015[54]	
	IgG_4-SC		*CC* (n=11)	*IgG_4-SC* (n=6)	*CC* (n=12)	*PSC* (n=10)	*IgG_4-SC* (n=35)	*PSC* (n=15)
	intrahepatic biliary ducts (n=16)	extrahepatic biliary ducts (n=9)						
Wall thickness (mm) *M±SD* *Me(IQR)*	2,3±0,4	2,6±0,3	3,3±1,2	3,7±0,9	2,8±0,6	2,6±0,9	2.5 (2.2–2.9)	2.4 (1.8–3.0)
Wall thickness (n): symmetric:asymmetric	11:4[1]	6:3[2]	1:9	6:0*	1:11*	2:8*	27:6*	1:14*
Outer margin (n): clear: unclear	15:0	9:0[2]	2:9	-	-	-	33:0*	2:13*
Inner margin (n):								
- smooth:irregular	15:0	9:0[2]	0:9	6:0*	1:11*	1:9*	33:0*	0:15*
- papillary	0	0	2	-	-	-	-	-
- diverticulum-like outpouching	-	-	-	-	-	-	0*	10*
Internal echo (n): homogeneous:heterogeneous	15:0[1]	9:0[2]	1:10	-	-	-	33:0*	7:8*
Extrinsic compression	1	0	0	-	-	-	2	0
Three layers structure (n): - preservation:disappearance	-	-	-	-	-	-	33:0*	0:15*

Note: IgG_4-SC — IgG_4-sclerosing cholangitis; PSC — primary sclerosing cholangitis; CC — cholangiocarcinoma.
[1]p <0.01 IgG_4-SC with intrahepatic biliary duct involvement vs CC
[2]p <0.01 IgG_4-SC with extrahepatic biliary duct involvement vs CC
*p <0.05

for patients with IgG_4-SC and concomitant type 1 AIP; however, this procedure was associated with a high risk of complications, such as pancreatitis, recurrent Hayem-Widal syndrome and papillitis [59].

Treatment

GCSs are a first-line therapy for remission induction in IgG_4-SC. A recommended GCS dose is 0.5–0.8 mg/kg/day per os (a standard starter prednisolone dose is 30–40 mg/kg/day) for 4 weeks with subsequent dose reduction by 5 mg once every 1–2 weeks [3, 45]. Results show that the average prednisolone dose (0.5–0.6 mg/kg) was as efficient as the high dose (0.8–1 mg/kg) for remission [60]. Given a high rate of relapses after GCS discontinuation (> 50 %) [24], studies recommend using a maintenance low-dose therapy with GCS (2.5–7.5 mg/day), for one to three years [61]. According to a retrospective analysis, maintenance therapy with low-dose prednisolone for over three years improved survival rates of patients with IgG_4-SC [62]. In case of insufficient response to GCS therapy or disease relapse, it is recommended to use immunosuppressants as a send-line therapy for remission maintenance [3]. This group of drugs includes thiopurines (azathioprine, 6-mercaptopurine), mycophenolate mofetil, methotrexate and calcineurin inhibitors (tacrolimus, cyclosporin A) [63–65]. A retrospective analysis to compare cyclophosphamide and mycophenolate mofetil did not demonstrate any superiority of one drug over the other in terms of remission induction [66]. Rituximab was prescribed to induce and maintain remission if GCS and steroid-sparing drugs were contraindicated, or if these agents were inefficient [67, 68]. According to a meta-analysis, complete response in 6 months was observed in 88.9 % (95 % CI 80.5–93.9), the rate of relapses was 21 % (95 % CI 10.5–40.3), median time to relapse was 10 months [67]. A higher relapse rate of 35.9 % (95 % CI 17.3–60.1) was recorded in patients with multisystemic damages (in addition to pancreas and/or bile ducts) [67]. Adverse events were observed in 25 % of patients: infusion reactions (8 patients), infectious complications (9 patients), hypogammaglobulimenia (1 patient), gall bladder cancer (1 patient) [67]. The rate of relapses after rituximab induction was

still high; the drug should be used with caution in IgG_4-SC, given the potential risk of infectious complications, such as bacterial cholangitis, cholecystitis and hepatic abscesses [12].

There are various approaches to the matter of bile duct stenting in patients with IgG_4-SC. In their study, Miyazawa M. et al. (2020) emphasise a higher risk of chololithiasis in patients who undergo stenting before GCS initiation [69]. Out of 69 patients with IgG_4-SC, only 41 patients received GCS without stenting and achieved clinical improvements, including 10 patients with obstructive jaundice [69]. The other 28 patients (40.6 %) underwent bile duct stenting before GCS initiation [69]. In this group, after successful GCS therapy, the stent was removed in 13 patients (46.4 %), while 10 patients (35.7 %) experienced spontaneous stent displacement [69]. During the follow-up period, three patients (4.3 %), who underwent stenting, had bile duct stones, while no patients after GCS therapy had this condition ($p = 0.032$) [69]. Another study demonstrated that the incidence of stenting-associated acute cholangitis was significantly lower in patients who had previous steroid therapy as compared to those who did not have any steroids (the incidence of no acute cholangitis in one month): 100 % vs 90 %; log-rank test $p = 0.0278$) [70].

Outcomes and Prognosis

Given the high efficacy of glucocorticosteroids, prognosis for patients with IgG_4-CS is favourable. 10–25 % of patients with IgG_4-SC can experience spontaneous remission [71]. The long-term prognosis is poorly studied; biliary cirrhosis is observed in 4.5–7.5 % of cases [72]; also, there are individual cases of portal hypertension [73] and one case of hepatic decompensation, requiring liver transplant [74]. Kensuke Kubota et al. (2023) conducted a retrospective data analysis of 924 patients with IgG_4-SC [62]. According to the study results, malignant neoplasms were recorded in 15 % (139/924) of patients: before IgG_4-CS developed — 48 cases, simultaneously with the diagnosis of IgG_4-SC or within 3 months after the diagnosis — 18 cases, after IgG_4-SC diagnosis — 83 cases [62]. In patients who had malignant neoplasms diagnosed significantly earlier than IgG_4-SC, it was most commonly localised in colon (27 %; 13 cases out of 48) and urinary system (25 %; 12 cases out of 48) [62]. Where cancer and IgG_4-SC were diagnosed at the same time, the most common malignancy was malignant neoplasm of the upper section of the GI tract (33 %; 6 cases out of 18) [62]. When cancer was diagnosed after the IgG_4-SC diagnosis, the most common cancer was urinary tract cancer (36 %; 30 cases out of 83), stomach and duodenum cancer (34 %; 28 cases out of 83) and colon cancer (28 %; 28 cases out of 83) [62]. Also, eight cases of bile duct cancer and nine cases of pancreatic cancer were diagnosed, all of them, but one, developed after IgG_4-SC. In the majority of cases, pancreatic cancer was diagnosed within 10 years after the diagnosis of IgG_4-SC, while bile duct cancer was diagnosed within two years [62]. Also, a multifactor analysis revealed that an IgG_4-SC relapse is an independent risk factor for malignancy [62]. Relapses were observed in 19.7 % (182/924) of patients [62]. Overall, the standardised incidence ratio (SIR) for MNPs after the diagnosis of IgG_4-SC was 12.68 (6.89–8.79) [62]. SIR values for bile duct and pancreatic cancer were 27.35 (23.39–31.12) and 18.43 (16.44–02.97), respectively [62]. Cumulative survival was statistically higher in patients who had maintenance steroid therapy ($p < 0.001$) [62]. Another retrospective study concluded that patients with IgG_4-SC are at a higher risk of malignancies, including pancreatic and bile duct cancer [5]. SIR for pancreatic and bile duct cancer was 10.30 and 8.88, respectively [5]. The risk of malignancies was high during the first year and five years after the IgG_4-SC diagnosis; SIR was 2.58 and 2.44, respectively [5].

Conclusion

IgG_4-SC is a rare condition which is challenging to diagnose; it can be mistaken for other bile duct diseases, such as PSC and CC. Diagnosis requires a comprehensive assessment of clinical, laboratory and instrumental data and often histological confirmation. In many cases, the condition is diagnosed after an assessment of the efficacy of a trial GCS therapy, usually with fast and positive response. Prognosis is favourable; however, life-long follow-up is required due to a high rate of relapses and a high risk of malignant transformation.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2024-14-2-108-115
УДК [616.9:578.834.1-06]:616-036.8-008.6
EDN: LEJDUX

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ПОСТКОВИДНЫЙ СИНДРОМ: ПЕРСИСТЕНЦИЯ СИМПТОМОВ И ФАКТОРЫ РИСКА (ПРОДОЛЬНОЕ ОБСЕРВАЦИОННОЕ ИССЛЕДОВАНИЕ)

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Post-COVID Syndrome: Persistence of Symptoms and Risk Factors (Longitudinal Observational Study)

Резюме

Цель исследования: изучение динамики симптомов постковидного синдрома (в зависимости от результатов полимеразной цепной реакции на SARS-CoV-2) и факторов, оказывающих на нее влияние. **Материалы и методы.** Исследование когортное, обсервационное продольное. I этап: одномоментный анализ медицинских карт пациентов с давностью COVID-19 12 мес. (анкета на постковидный синдром, анализы крови). II этап: повторное анкетирование, давность заболевания — 24 мес. Выделены тестовая (положительная полимеразная цепная реакция, 138 чел.) и контрольная (отрицательная полимеразная цепная реакция, 87 чел.) группы. Статистический анализ: пакет Statistica 13.5.0.17. **Результаты.** Через 1 год после COVID-19 частота проявлений постковидного синдрома составила (тестовая *vs* контрольная группы): астения 63 % *vs* 64 %; снижение качества жизни 59 % *vs* 56 %; респираторный синдром 60 % *vs* 49 %; артралгии 55 % *vs* 49 %; кардиальный синдром 47 % *vs* 46 %, (разница не достоверна); симптомы, связанные с женским полом (r=0,231-0,379), тяжестью COVID-19 (r=0,187-0,425); Д-димер (r=0,244-0,328). Через 2 года частота симптомов составила: астения 43 % *vs* 45 %; кардиальные симптомы 23 % *vs* 15 %; респираторные симптомы 18 % *vs* 22 %; кожные проявления 8 % *vs* 12 %; снижение качества жизни 7 % *vs* 9 %, разница не достоверна; симптомы, связанные с возрастом (r=0,208-0,402). На протяжении двух лет симптомы коррелировали с тромбоцитами (r=-0,322-0,403), ферментами печени (r=0,216-0,298), липидами крови (r=0,188-0,257). **Заключение.** Выраженность постковидного синдрома не зависит от результатов полимеразной цепной реакции на SARS-CoV-2. Частота кардиальных и респираторных синдромов через 2 года снижается в 2-3 раза; качество жизни улучшается. Астения — самый долгосрочный синдром. Факторы риска постковидного синдрома в течение 1-го года — тяжесть COVID-19, женский пол, уровень Д-димера; со 2-го года — возраст. В течение двух лет после COVID-19 требуется контроль ферментов печени, липидного спектра, тромбоцитов.

Ключевые слова: *постковидный синдром, динамика, полимеразная цепная реакция, факторы риска*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 01.02.2024 г.

Принята к публикации 11.03.2024 г.

Для цитирования: Агафонова Т.Ю., Еловикова Н.Н., Бронникова О.В. и др. ПОСТКОВИДНЫЙ СИНДРОМ: ПЕРСИСТЕНЦИЯ СИМПТОМОВ И ФАКТОРЫ РИСКА (ПРОДОЛЬНОЕ ОБСЕРВАЦИОННОЕ ИССЛЕДОВАНИЕ). Архивъ внутренней медицины. 2024; 14(2): 108-115. DOI: 10.20514/2226-6704-2024-14-2-108-115. EDN: LEJDUX

Abstract

The aim — studying the dynamics of symptoms of post-COVID syndrome (depending on the results of depending on the results of the polymerase chain reaction for SARS-CoV-2) and the factors influencing it. **Materials and methods.** A study is a cohort, observational longitudinal. Stage I: snapshot analysis of medical records of patients with COVID-19 disease history 12 months. (questionnaire for post-COVID syndrome, blood tests). Stage II: questionnaire repeat, disease history — 24 months. There were test (positive polymerase chain reaction, 138 people) and control (negative polymerase chain reaction, 87 people) groups. Statistical analysis: package Statistica 13.5.0.17. **Results.** 1 year after COVID-19, the frequency of manifestations of post-COVID syndrome was (test vs control group): asthenia 63 % vs 64 %, decreased quality of life 59 % vs 56 %, respiratory syndrome 60 % vs 49 %, arthralgia 55 % vs 49 %, cardiac syndrome 47 % vs 46 % (the difference is not significant); symptoms are associated with female gender (r=0.231-0.379), severity of COVID-19 (r=0.187-0.425), D-dimer (r=0.244-0.328). After 2 years, the frequency of symptoms was: asthenia 43 % vs 45 %, cardiac symptoms 23 % vs 15 %, respiratory symptoms 18 % vs 22 %, skin manifestations 8 % vs 12 %, decreased quality of life 7 % vs 9 %, the difference is not significant; symptoms are associated with age (r=0.208-0.402). During two years, symptoms have been correlating with platelets (r=-0.322-0.403), liver enzymes (r=0.216-0.298), blood lipids (r=0.188-0.257). **Conclusions.** The severity of post-COVID syndrome does not depend on the results of the polymerase chain reaction for SARS-CoV-2. The frequency of cardiac and respiratory syndromes after 2 years decreases by 2-3 times; quality of life improves. Asthenia is the most long-term syndrome. Risk factors for post-COVID syndrome during the 1st year — severity of COVID-19, female gender, D-dimer level; from the 2nd year — age. For two years after COVID-19, monitoring of liver enzymes, lipids, and platelets is required.

Key words: *post-COVID syndrome, dynamics, polymerase chain reaction, risk factors*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 01.02.2024

Accepted for publication on 11.03.2024

For citation: Agafonova T.Yu., Elovikova N.N., Bronnikova O.V. et al. Post-COVID Syndrome: Persistence of Symptoms and Risk Factors (Longitudinal Observational Study). The Russian Archives of Internal Medicine. 2024; 14(2): 108-115. DOI: 10.20514/2226-6704-2024-14-2-108-115. EDN: LEJDUX

ALT — alanine aminotransferase, AST — aspartate aminotransferase, LDH — lactic dehydrogenase, LDL — low density lipoproteins, NCVI — novel coronavirus infection, PCR — polymerase chain reaction, COVID-19 — COronaVIrus Disease 2019, SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2

Introduction

The term "post-COVID syndrome" is used to describe persistent or new symptoms arising three months after acute COVID-19 and not associated with alternative diagnoses [1, 2]. The incidence of post-COVID syndrome varies significantly — from 10-20 % (according to the WHO) to 60–80 % (meta-analyses and original studies) [3-5]. The significant difference in the information on the incidence of post-COVID syndrome is a result of its high clinical heterogeneity, as well as the lack of a unified and specific definition of this condition.

Various clinical symptoms comprising post-COVID syndrome are grouped into clusters (cognitive, neural and mental, cardiac and respiratory, digestive, asthenic, etc) [6]. Several risk factors of this syndrome have been identified; they are elderly age, higher body mass index, comorbidities, specific symptoms of acute COVID-19 (particularly dyspnoea), number of symptoms during the acute phase, and female sex [3, 7, 8].

It has been demonstrated that over time the incidence of symptoms reduces significantly; however, 6, 12, 18, and 24 months after COVID-19 diagnosis, the share of patients with at least one symptom is 32.3 %, 30.5 %, 25.8 %, and 33.3 %, respectively [9]. According to authors, the most long-lasting consequences of COVID-19 (with the longest follow-up period of 20 months) are sleep disorders, depression, paresthesia [6], hyposmia and fatigue [10], changes of skin and mucous membranes, excessive sweat, oedema [11]; the most long-lasting symptoms were found in women aged 20 years old and over [4].

There are evidences on the relationship between the severity of clinical manifestations of post-COVID syndrome and laboratory test results: D-dimer, markers of inflammation and hepatic cytolysis [8, 12], as well as the presence of positive polymerase chain reaction (PCR) to SARS-CoV-2 during the acute phase of the disease [13]. Therefore, continued observational studies of

post-COVID syndrome are of some interest: identification of its maximum duration and risk factors of symptom persistence.

Study objective: To study the changes in symptoms of post-COVID syndrome (depending on SARS-CoV-2 PCR results) and impacting factors.

Materials and Methods

Study type: cohort, observational longitudinal study. The study was conducted in the City Polyclinic LLC (Perm). The study consisted of two stages.

Stage one: a snapshot analysis of 447 medical records of outpatient patients aged 19 to 91 years old, who underwent comprehensive medical examination during a period from July 2021 to October 2022 (Order No. 698н of the Ministry of Health of the Russian Federation dated 01 July 2021, On the Approval of the Procedure of Citizen Referrals to a Comprehensive Medical Examination, Including Categories of Citizens Who Undergo a Priority Comprehensive Medical Examination. [Digital resource]. Garant.ru, informational and legal web portal, 1990–2021. Electronic data https://www.garant.ru/products/ipo/prime/doc/401344234/ (accessed on 25 January 2024) and had novel coronavirus infection (NCVI). All subjects were divided into two subsets: study subset with positive SARS-COV-2 PCR (227 subjects) and controls — with negative PCR (200 subjects). On the average, subjects had COVID-19 12 months before medical examination. Questionnaires for post-COVID syndrome identification [13], biochemical and clinical test results were evaluated.

Stage two: repeated questionnaires of subjects included in stage one in order to identify symptoms of post-COVID syndrome (phone calls). Response was provided by 138 subjects (61 %) in the PCR-positive subset and 87 subjects (44 %) in the PCR-negative subset, thus defining the final size of the study and control groups for descriptive and comparative statistics. During repeated questionnaires, the average time after recovery after COVID-19 was 24 months. The characteristics of groups are presented in Table 1.

The study group and controls are comparable in terms of age, sex, severity and time of NCVI.

Ethics. All patients provided their written consent for personal data processing upon inclusion in the advanced medical examination program.

Statistical analysis. Quantitative test parameters with non-normal distribution are presented as median (Me), 25(Q25) and 75(Q75) percentiles — Me (Q25–Q75 %), while qualitative variables are presented as percentage of an absolute number of patients in the groups. Statistical data processing was performed using the Kolmogorov–Smirnov test, Mann-Whitney test, Pearson's X^2 (comparison of frequencies in independent groups), McNemar test (comparison of frequencies in repeated questionnaires), Spearman's rank correlation in Statistica 13.5.0.17 application.

Results and Discussion

Laboratory test results from stage one of the study are presented in *Table 2*. Creatinine values in the study group were higher than in controls; nevertheless, they are within the normal range. The blood count was comparable in both groups.

Information from primary (stage one of the study) and repeated questionnaires (stage two of the study), as well as a comparative analysis of the incidence of subjective symptoms of post-COVID syndrome in patients with positive and negative PCR results, is presented in *Table 3*. The most common manifestations in primary questionnaires (on the average, 12 months after COVID-19) in both groups were symptoms of asthenic and respiratory clusters, as well as poorer quality of life and articular syndrome. Also, almost a half of respondents in the study group had anosmia and loss of taste, while the most common symptom in controls was cardiac syndrome.

Repeated questionnaires (on the average, 24 months after acute NCVI) demonstrated similar trends in persistence of post-COVID syndrome manifestations: the top five most common manifestations were asthenic, respiratory clusters, cardiac syndrome, skin symptoms and poorer quality of life. Nevertheless, there was a shift in accents within a set of symptoms: two years after NCVI, cardiac symptoms and respiratory manifestations were on the second place (in terms of incidence) after asthenic syndrome in the study group and controls, respectively. It is also worth mentioning that, while during the first year after acute COVID-19, poorer quality of life (second place in terms of incidence after physical and mental asthenia) was a dominant symptom, two years after the disease it shifted to the fifth place, and articular syndrome was less common than skin manifestations in both groups.

Table 1. *Characterization of the test and control groups*

Parameter	Test group, n=138	Control group, n=87	p
Number of men, *abs. (%)*	27 (20)	18 (21)	>0,1
Age, years, *Me (Q25-75 %)*	61 (47-70)	59 (44-67)	0,199
Mild severity of COVID-19, *abs. (%)*	59 (43)	49 (56)	>0,1

Note: p — level of significance of difference

Table 2. *Blood parameters of patients with laboratory confirmed (test group) and unconfirmed (control group) COVID-19*

Parameter	Test group, n=138	Control group, n=87	p
	Me (Q25-75 %)		
Clinical blood test			
Red blood cells, $x10^{12}$/L	4,4 (4,3-4,8)	4,5 (4,3-4,7)	0,606
Hemoglobin, g/l	134 (125-138)	133 (126-140)	0,769
Platelets, $x10^{9}$/L	235 (210-270)	246 (216-270)	0,041
Leukocytes, $x10^{9}$/L	6,3 (5,6-7,0)	6,2 (5,6-7,3)	0,882
ESR, mm/h	12 (7-15)	10 (7-14)	0,075
Blood chemistry			
ALT, U/L	18,7 (14,9-23,9)	17,4 (12,0-25,5)	0,262
AST, U/L	20,0 (17,2-24,4)	19,2 (17,3-23,0)	0,759
Glucose, mmol/l	5,1 (4,8-5,6)	5,0 (4,6-5,5)	0,102
β-lipoproteins, mmol/l	3,0 (2,3-3,8)	3,3 (2,6-4,0)	0,296
Cholesterol, mmol/l	5,2 (4,5-6,2)	5,4 (4,7-6,1)	0,530
Creatinine, μmol/l	90,0 (83,7-95,0)	89,0 (86,0-97,0)	0,004
LDH, U/L	184,9 (161,3-206,3)	187,5 (164,6-216,3)	0,449
D-dimer, ng/ml	0,36 (0,2-0,5)	0,31 (0,21-0,48)	0,283

Note: p — level of significance of difference

Table 3. *Survey data of patients with laboratory confirmed (test group) and unconfirmed (control group) COVID-19 to identify post-COVID syndrome*

Parameter	Test group, n=138	Control group, n=87	p
Primary survey			
Fatigue, muscle pain, dysautonomia, cognitive deficit, %	63,0	64,4	0,841
Decreased quality of life and performance, %	59,4	56,3	0,558
Shortness of breath, exercise intolerance, cough, %	56,5	49,4	0,115
Joint pain, %	55,1	49,4	0,409
Anosmia, ageusia, %	50,7	42,5	0,707
Chest pain, tachycardia, leg swelling, %	48,6	46,0	0,707
Hair loss, skin rash, %	42,0	32,2	0,139
Diabetes mellitus: newly diagnosed, unstable hyperglycemia, %	14,5	12,6	0,695
Temperature increase, %	13,8	14,9	0,806
Repeated survey			
Fatigue, muscle pain, dysautonomia, cognitive deficit, %	42,8	44,8	0,760
Chest pain, tachycardia, leg swelling, %	23,2	14,9	0,132
Shortness of breath, exercise intolerance, cough,%	18,1	21,8	0,493
Hair loss, skin rash, %	8,0	11,5	0,376
Decreased quality of life and performance, %	7,2	9,2	0,600
Joint pain, %	6,5	4,6	0,547
Anosmia, ageusia, %	5,1	2,3	0,301
Diabetes mellitus: newly diagnosed, unstable hyperglycemia, %	0,0	0,0	-
Temperature increase, %	0,0	0,0	-

Note: p — level of significance of difference

Changes in subjective manifestations of post-COVID syndrome during the year are presented in Figures 1 and 2. Study and control subjects had significantly fewer symptoms (even high temperature and hyperglycemia resolved), except for physical and mental asthenia. The examined cohort demonstrated similar changes in symptoms.

The most significant reliable relations between post-COVID syndrome manifestations and examined factors are presented in *Table 4*. Of note, the existence of symptoms one year after acute COVID-19 is greatly impacted by being a female in the study group, severity of past NCVI and D-dimer values in both groups.

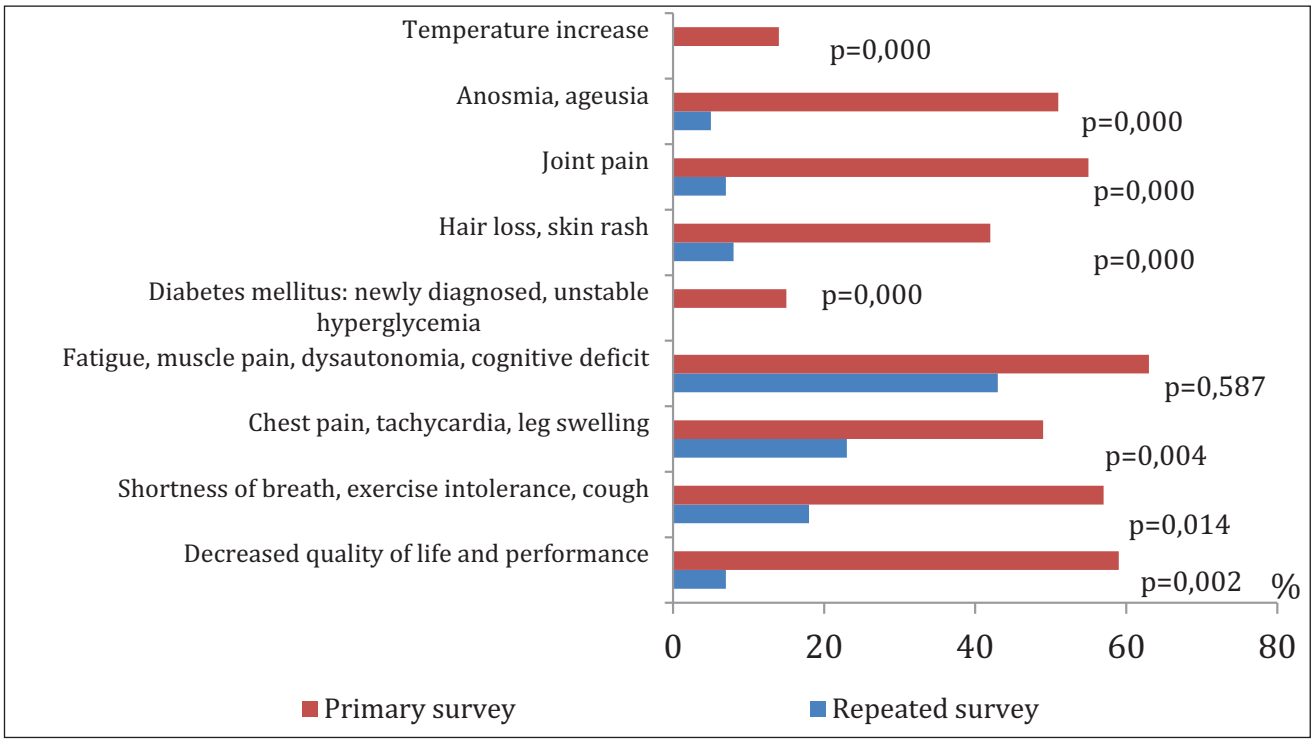

Figure 1. *Dynamics of symptoms of post-Covid syndrome in laboratory-confirmed (test group) SARS-CoV-2 infection*

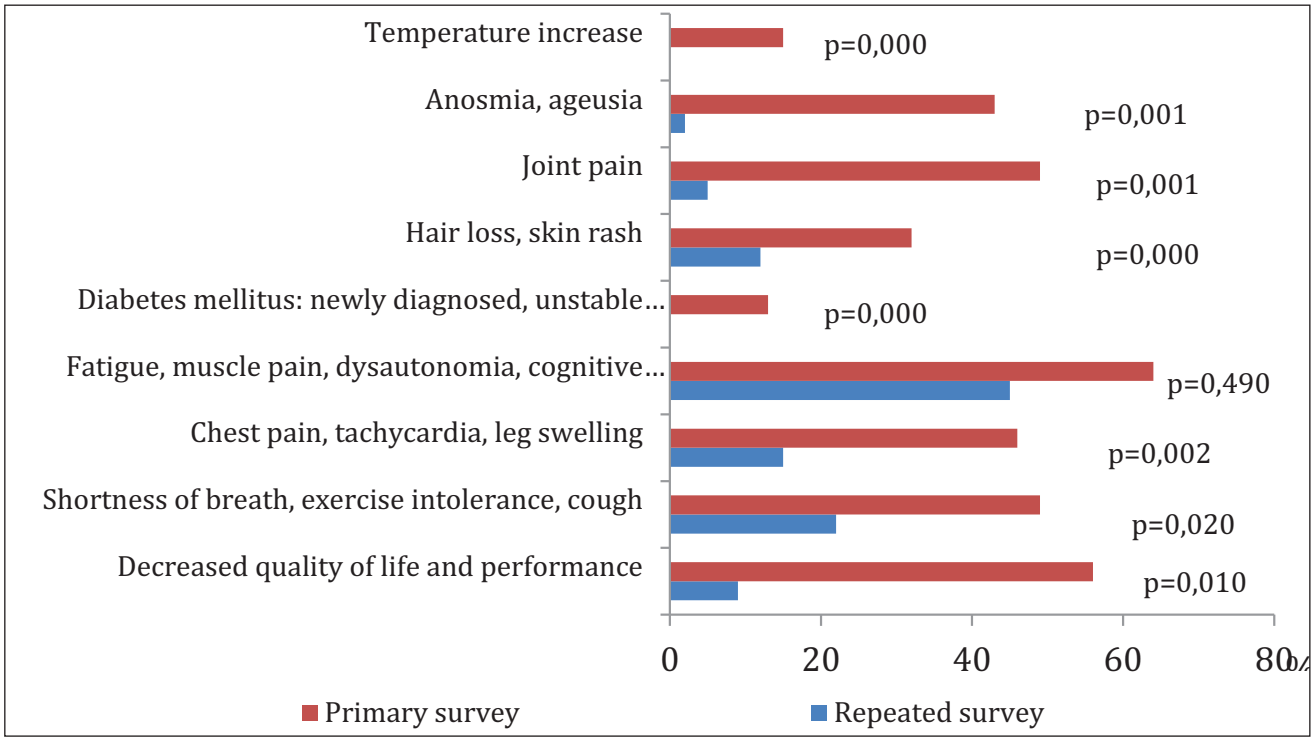

Figure 2. *Dynamics of symptoms of post-Covid syndrome in laboratory-unconfirmed (control group) SARS-CoV-2 infection*

Table 4. *Correlation analysis of manifestations of post-COVID syndrome in patients with laboratory confirmed (test group) and unconfirmed (control group) SARS-CoV-2 infection*

Parameter	Correlation coefficients in the test group/control group, *r, p <0,05*						
	Fatigue, muscle pain, dysautonomia, cognitive deficit	Decreased quality of life and performance	Shortness of breath, exercise intolerance, cough	Joint pain	Chest pain, tachycardia, leg swelling	Anosmia, ageusia	Hair loss, skin rash
Gender	0,379/-	0,374/-	0,231/-	0,289/-	0,296/-	0,281/-	0,309/ 0,230
Age	0,402/ 0,223	-	-	-	0,208/ 0,235	-/0,237	-
Severity of COVID-19	-/0,329	0,285/ 0,349	-/0,406	0,187/ 0,425	0,182/ 0,311	-/0,265	0,288 /0,226
Platelets	-/-0,370 -0,403/-	-	-/-0,347	-	-/-0,322	-	-
Alaninaminotransferase, Aspartataminotransferase, Lactate dehydrogenase	0,216/-	-/0,229 0,249/-	-/0,258	-/0,298	-/0,220 0,244/-	-	-/0,222
Cholesterol, β-lipoproteins	-/0,224	0,257/-	0,188/-	0,212/-	-	-	-
D-dimer	0,244/-	-	0,308/0,315	-	-/0,328	-	-/0,328

Note: correlation coefficients identified at the 2nd stage of the study are highlighted in red

Two years later, symptom prolongation is affected by age (asthenic, cardiac syndromes in both groups, loss of taste and anosmia in controls). During a two-year follow-up period, platelet count, hepatic enzymes and blood lipids still impact subjective manifestations of post-COVID syndrome. Lower platelet count in controls is associated with asthenic and respiratory syndromes during the first year, with cardiac syndrome two years after the acute phase; in the study group — with asthenia persisting for two years. Hepatic cytolysis is related to the major symptoms during the first year in controls and the second year in the study group; the quality of life and cardiac syndrome are affected the most. Total cholesterol and LDL levels are related to the quality of life, respiratory and articular syndromes in the study group and with asthenic syndrome in the control group (two years after NCVI).

Overall, the results of our study did not conflict to the literature data; however, there are some clarifications and updates. According to available reviews, during the first year after acute NCVI, the incidence of the most common signs of post-COVID syndrome are: physical and mental asthenia is recorded in 46–67 %, loss of taste and anosmia — in 27–41 %, respiratory symptoms — in 15–37 %, cardiac symptoms — in 31 % [6, 10, 11], joint pain — in 39 % [5]. In examined patients, the incidence of symptoms was slightly higher than the mentioned value and did not depend on SARS-CoV-2 PCR results. The high incidence of post-COVID syndrome resulted in significantly lower quality of life and disability during the first year after NCVI in over a half of patients.

During the second year after acute COVID-19, the incidence of subjective symptoms was considerably lower, except physical and mental asthenia, which can be considered the most prolonged manifestation of post-COVID syndrome. Lower severity of manifestations and adaptation to the condition over time made socialisation of post-NCVI patients possible, thus the number of patients who reported poorer quality of life dropped 6–7-fold. Unfortunately, the number of studies with the longest follow-up period of post-COVID-19-patients of 20–24 months is limited; nevertheless, they also demonstrate long-lasting signs of fatigue and cognitive disorders [3, 6]. Long-lasting post-COVID symptoms also include cardiac, respiratory and skin clusters. The latter is less common than articular syndrome during the first year after recovery; however, it is more persistent. Long-lasting NCVI manifestations are associated with delayed immune clearance of SARS-CoV-2 antigen or a high viral load during acute COVID-19 [14]. The latter is doubtful, since we have not found any difference in manifestation of post-COVID syndrome in patients with laboratory-proven and not confirmed SARS-CoV-2 infection. However, negative PCR results during the acute phase can be caused not only by test system faults, but also a low viral load.

There are some indications in literature that subjective signs of post-COVID manifestations last for 7–12 months in hospitalised patients and 4 months in non-hospitalised patients, thus confirming the relationship between symptoms persistence and severity of the acute phase [4]. This study has also established the relationship between post-COVID syndrome and NCVI

severity in both groups. On the other hand, acute phase severity matters only for the number of manifestations of post-COVID syndrome during the first year, thus probably explaining the difference in test results: some studies claim that disease severity does not impact long-lasting COVID-19 [9, 10].

In our study, female sex, which the majority of authors include in risk factors of post-COVID syndrome [2, 4, 7, 9], is a risk factor only during the first year after an acute infection; during the second year, persistent symptoms (particularly astehnia, cardiac symptoms, anosmia, loss of taste) are associated with age, which can be due to slower recovery and adaptation in older patients.

It is worth mentioning that, 12 months after NCVI, blood counts, blood biochemistry and D-dimers normalise, irrespective of baseline values during the acute phase and laboratory confirmation of NCVI. However, persistent post-COVID syndrome is affected by platelets count (negative correlation coefficient), LDH, AST, ALT, cholesterol and LDL, D-dimer (positive correlation coefficients), while the latter impacts the presence of subjective symptoms only during the first year after NCVI, all other parameters — during two years. These parameters make sense for several years for the purposes of assessing the long-term residual organ damage (lungs, heart, central nervous system, peripheral nervous system), since, for instance, it has been proven that the cardiovascular risk rises even one year after an acute disease, irrespective of long-lasting symptoms of COVID-19 [15].

Currently, multicenter, cohort studies are ongoing, which assess post-NCVI patients [2], the results of which will add to the data on the duration and signs of post-COVID syndrome, standardise test methods and identify approaches to patient management.

Conclusions

1. The incidence of signs of post-COVID syndrome does not depend on PCR results during acute SARS-CoV-2 infection.
2. Symptoms of post-COVID syndrome persist for at least two years; during the entire follow-up period, the main signs are: asthenia, cardiac and respiratory clusters, poorer quality of life, articular syndrome (the latter is less common than skin manifestations after the first year).
3. Physical and mental asthenia is the most long-lasting manifestation of post-COVID syndrome, its incidence does not reduce after two years after the acute phase and persists practically in a half of all patients.
4. After two years after COVID-19, the incidence of the main manifestations of post-COVID syndrome (cardiac and respiratory clusters) drops 2–3-fold; poorer quality of life is 6–7 times less common.
5. The risk factors for post-COVID syndrome are severity of acute NCVI and female sex during the first year, after that — age.
6. D-dimer is associated with subjective signs of post-COVID syndrome during one year after the acute phase; hepatic enzymes, lipid profile and platelet count should be monitored for at least two years.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2024-14-2-116-123
УДК 616.61-002.2-07-053.9
EDN: MOMXRZ

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ВКЛАД ПАТОЛОГИИ ПОЧЕК В РАСЧЕТНУЮ СКОРОСТЬ КЛУБОЧКОВОЙ ФИЛЬТРАЦИИ У ПАЦИЕНТОВ СТАРШЕЙ ВОЗРАСТНОЙ ГРУППЫ

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Chronic kidney disease in older patients: the contribution of kidney pathology to the estimated glomerular filtration

Резюме

Цель — оценить значение вклада патологии почек в расчетную скорость клубочковой фильтрации и его прогностическое значение у пациентов пожилого и старческого возраста. **Материалы и методы.** Обследовано 472 пациента (241 женщина и 231 мужчина, средний возраст 69,6±7,3 лет) со стабильной сердечно-сосудистой патологией пожилого и старческого возраста. ХБП наблюдалась у 302 (63,9 %) пациентов пожилого и старческого возраста. Расчетную скорость клубочковой фильтрации (рСКФ) определяли, используя уравнение CKD-EPI (модификация 2011). Вклад патологии почек (ВПП) в рСКФ рассчитывали по разнице между «реальной» рСКФ (рассчитанной по формуле CKD-EPI, 2011 на основании «реального» креатинина сыворотки) и прогнозируемой для данного возраста и пола рСКФ (патент № RU 2723748 C1). Срок наблюдения составил 12 месяцев. В качестве первичной конечной точки оценивалась общая смертность. **Результаты.** ВПП в рСКФ у пациентов пожилого и старческого возраста составил 26,3 (14,9;35,7) %, увеличиваясь с тяжестью ХБП. ВПП в рСКФ у пациентов пожилого и старческого возраста с ХБП не различался в зависимости от пола и возраста (p >0,05). Модифицированный индекс коморбидности Чарлсон был более высоким у пациентов с ХБП с ВПП в рСКФ более 43,3 % по сравнению с пациентами с ВПП в рСКФ менее 43,3 (p=0,004). ВПП в рСКФ более 43,3 % ассоциировался с риском смерти в течение года у пациентов с ХБП (ОР 4,7; 95 % ДИ 1,99–10,9; p<0,0001). При оценке прогностического значения ВПП в рСКФ независимо от наличия ХБП установлено, что увеличение ВПП в рСКФ более 17,9 % ассоциировано с риском смерти в течение года у пациентов пожилого и старческого возраста со стабильной сердечно-сосудистой патологией (ОР 2,47; 95 % ДИ 1,31–4,67; p=0,004). **Заключение.** ВПП в рСКФ у пациентов пожилого и старческого возраста с ХБП и стабильной сердечно-сосудистой коморбидностью увеличивается с тяжестью ХБП и не зависит от пола и возраста. У пациентов пожилого и старческого возраста со стабильной сердечно-сосудистой патологией ВПП в рСКФ имеет прогностические преимущества при оценке годовой летальности по сравнению с оценкой рСКФ по формуле CKD EPI (2011).

Ключевые слова: *хроническая болезнь почек, вклад патологии почек, пациенты пожилого и старческого возраста*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 22.01.2024 г.
Принята к публикации 14.03.2024 г

Для цитирования: Ефремова Е.В., Шутов А.М., Кузнецова Т.С. **ВКЛАД ПАТОЛОГИИ ПОЧЕК В РАСЧЕТНУЮ СКОРОСТЬ КЛУБОЧКОВОЙ ФИЛЬТРАЦИИ У ПАЦИЕНТОВ СТАРШЕЙ ВОЗРАСТНОЙ ГРУППЫ**. Архивъ внутренней медицины. 2024; 14(2): 116-123. DOI: 10.20514/2226-6704-2024-14-2-116-123. EDN: MOMXRZ

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Abstract

The purpose of the study was to assess the contribution of kidney pathology to the estimated glomerular filtration rate and its prognostic value in elderly and senile patients. **Materials and methods.** 472 elderly and senile age patients (241 women and 231 men, mean age 69.6±7.3 years) with stable cardiovascular diseases were examined. CKD was observed in 302 (63.9 %) elderly and senile patients. Estimated glomerular filtration rate (eGFR) was determined using the CKD-EPI equation (modified 2011). The contribution of kidney pathology (CKP) to eGFR was calculated by the difference between the "real" eGFR (calculated using the CKD-EPI, 2011 formula based on the "real" serum creatinine) and the predicted eGFR for a given age and sex (patent No. RU 2723748 C1). The follow-up period was 12 months. The primary endpoint was overall mortality. **Results.** The CKP in eGFR in elderly and senile patients was 26.3 (14.9;35.7) %, increasing with the severity of CKD. The CKP in eGFR in elderly and senile patients with CKD did not differ depending on gender and age (p>0.05). The modified Charlson comorbidity index was higher in patients with CKD with CKP in eGFR more than 43.3 % compared to patients with The CKP in eGFR less than 43.3 (p = 0.004). The CKP in eGFR more than 43.3 % was associated with a 1-year risk of death in patients with CKD (OR 4.7; 95 % CI 1.99–10.9; p<0.0001). When assessing the prognostic value of CKP in eGFR, regardless of the CKD it was found that an increase CKP in eGFR more than 17.9 % was associated with a 1-year risk of death in elderly and senile patients with stable cardiovascular diseases (OR 2.47; 95 % CI 1.31–4.67; p=0.004). **Conclusion.** The CKP in eGFR in elderly and senile patients with CKD and stable cardiovascular comorbidity increases with the severity of CKD and does not depend on gender and age. In elderly and senile patients with stable cardiovascular diseases, the CKP in eGFR has prognostic advantages when assessing annual mortality compared to eGFR assessment using the CKD EPI formula (2011).

Key words: *chronic kidney disease, contribution of kidney pathology, elderly and senile patients*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 22.01.2022
Accepted for publication on 14.03.2024

For citation: Efremova E.V., Shutov A.M., Kuznetsova T.S. The contribution of kidney pathology to the estimated glomerular filtration rate in older age group patients. The Russian Archives of Internal Medicine. 2024; 14(2): 116-123. DOI: 10.20514/2226-6704-2024-14-2-116-123. EDN: MOMXRZ

AH — arterial hypertension, CABG — coronary artery bypass grafting, BP — blood pressure, RPC — renal pathology contribution, CI — confidence interval, IHD — ischemic heart disease, MI — myocardial infarction, CInd — comorbidity index, ACE — acute cerebrovascular event, OR — odds ratio, eGFR — estimated glomerular filtration rate, AF — atrial fibrillation, CKD — chronic kidney disease, CHF — chronic heart failure, PCI — percutaneous coronary intervention.

Introduction

The key causes of a chronic disease are still arterial hypertension and diabetes mellitus [1, 2]. Age is an independent non-modifiable risk factor for chronic kidney disease (CKD) development and progression, with chronic kidney disease being a sign of premature ageing [3, 4]. In elderly and old patients, CKD is not always timely diagnosed and is often seen as age-related changes of the renal function [5]. Some authors propose introducing a term "age-related deterioration in renal function" in order to prevent a hike in the incidence of CKD in elderly patients [6]. At the same time, despite any age-related changes, reduction in glomerular filtration rate is not mandatory in healthy population [7].

The varying significance of the age factor needs to be taken into account: younger patients with eGFR of less than 45 mL/min/1.73 m^2 have a higher risk of end-stage kidney failure; on the contrary, in 85-year-old patients, the risk of death outweighs the risk end-stage kidney failure irrespective of the eGFR value [8]. It is worth mentioning that in elderly patients, CKD is usually diagnosed due to an isolated reduction in estimated glomerular filtration rate and not albuminuria [9, 10]. Estimated glomerular filtration rate will not allow assessing the contribution from pathology to eGFR, since this parameter also includes age-related reduction in renal function.

Study objective: To assess the significance of renal pathology contribution to the estimated glomerular filtration rate and its prognostic value in elderly and old patients.

Materials and Methods

We examined 472 elderly and old patients (241 female and 231 male patients, mean age: 69.6 ± 7.3 years old) with a stable cardiovascular pathology. Elderly patients were aged 60–74 years old, while old patients were aged 75–89 years old, according to the World Health Organisation's criteria (2012) [11].

The study is an open-label, prospective, cohort study using continuous sampling method. Exclusion criteria were: acute cardiovascular pathology (acute myocardial infarction, instable angina, decompensated cardiac failure, acute cerebrovascular event within six months prior to enrolment); end-stage renal disease requiring replacement renal therapy, clinically apparent hepatic failure, acute infectious diseases and/or chronic disease relapses, mental disorders, apparent cognitive disorders which hinder tests, absence of the informed consent to take part in the study. The follow-up period was 12 months. Overall mortality was the primary endpoint.

CKD was diagnosed in accordance with the National Guidelines on the Key Principles of Screening, Diagnosis, Prevention and Management of Chronic Kidney Disease (Russian National Society of Nephrology, 2012) [12]. The analysis took into account the Clinical Guidelines

on the Chronic Kidney Disease (Russian Nephrology Association, 2021) [2].

Estimated glomerular filtration rate (eGFR) was determined using a formula proposed by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration, 2011 modification). Renal pathology contribution (RPC) to estimated glomerular filtration rate (eGFR) was calculated on the basis of the difference between the actual eGFR (calculated using CKD-EPI, 2011 formula on the basis of the real blood creatinine value) and eGFR value predicted for a specific age and sex, assuming that serum creatinine is 80 μmol/L for women and 100 μmol/L for men (Patent No. RU 2723748 C1), formula (1).

$$A\ (\%) = (B\text{-}C)*100\ \% / B, \quad (1)$$

where A is renal pathology contribution to estimated glomerular filtration rate;

B is a predicted (optimal) estimated glomerular filtration rate;

C is the real estimated glomerular filtration rate.

Cardiovascular pathologies were diagnosed in accordance with the current Russian guidelines.

Clinical characteristics of subjects are presented in Table 1.

Chronic kidney disease was diagnosed in 302 (63.9 %) of elderly and old patients. More common was CKD with eGFR of less than 60 mL/min/1.73 m2 — 277 patients (91.7 %) out of 302. CKD was diagnosed on the basis of an isolated reduction in eGFR below 60 mL/min/1.73 m2 — in 218 CKD patients (72.2 %). Structural renal changes were observed in 67 CKD patients (22.2 %), albuminuria/proteinuria — in 62 CKD patients (20.5 %) (n = 302). Thus, there were no cases of stage 1 CKD; stage 2 CKD was diagnosed only in 25 patients (8.3 %), stage 3a was observed in 185 patients (61.3 %), 3b — in 83 patients (27.5 %), stage 4 — in 9 patients (2.9 %) of elderly and old age (n = 302).

Comorbidity was assessed in accordance with the Clinical Guidelines on Comorbid Pathologies in Clinical Practice [13], modified Charlson comorbidity

Table 1. *Clinical characteristics of elderly and senile patients with stable cardiovascular diseases*

Parameters	n=472
Women, n (%)	241(51)
Men, n (%)	231(49)
Age (M±SD, years)	69,6±7,3
Location:	
urban residents, n (%)	415(87,9)
rural residents, n (%)	57(12,1)
Smoking, n (%)	55(11,7)
Heredity for cardiovascular pathology, n (%)	205(43,4)
AH, n (%)	452 (95,8)
CHF, n (%)	335 (70,1)
CAD, n (%)	349 (74)
including history of myocardial infarction, n (%)	132 (27,9)
History of PCI/CABG, n (%)	54 (11,4)
AF, (n%)	156 (33)
including permanent AF, n (%)	81 (17,2)
Diabetes mellitus type 2, n (%)	129 (27,3)
Peripheral artery disease, n (%)	70 (14,8)
History of stroke, n (%)	60 (12,7)
Non-coronary heart diseases (cardiomyopathies, heart defects), n (%)	48 (10,2)
Pathology of the musculoskeletal system, n (%)	275 (58,2)
Obesity, n (%)	200 (42,4)
Dementia, n (%)	97 (20,5)
Anemia, n (%)	92 (19,1)
Pathology of the thyroid gland, n (%)	73 (15,4)
Primary kidney diseases (chronic glomerulonephritis, chronic pyelonephritis, urolithiasis), n (%)	67 (14,2)
Chronic nonspecific lung diseases (chronic obstructive pulmonary disease, bronchial asthma), n (%)	47 (9,9)
Peptic ulcer, n (%)	27 (5,7)
Connective tissue diseases, n (%)	19 (4,0)
Malignant tumors without metastases (complete remission >5 years are excluded), n (%)	18 (3,8)
History of viral hepatitis, n (%)	11 (2,3)

Notes. AH — arterial hypertension, CABG — coronary artery bypass grafting, CAD — coronary artery disease, CI — comorbidity index, ACVA — acute cerebrovascular accident, AF — atrial fibrillation, CKD — chronic kidney disease, CHF — chronic heart failure, PCI — percutaneous coronary intervention

index (CInd) was used (Patent No. RU 2706975 C1) [10]. Comorbidity was high is CInd was more than 6 points.

Statistical data analysis was performed using StatSoft-Statistica v.10.0.1011.6 (StatSoft, Inc, USA) and MedCalc 11.6 (MedCalc Software Ltd, Belgium). Data distribution was assessed using Shapiro–Wilk's W test. Depending on analysis results, data were presented as M±SD, where M is the arithmetic mean, SD is standard deviation (in normal distribution), or Me (IQR), where Me is median, IQR is interquartile range: 25th percentile–75th percentile (in a distribution other than normal). Groups were compared using Student t-test and Mann–Whitney U test) (in a distribution other than normal). Test method accuracy was assessed using ROC analysis; event probability was predicted using logistic regression analysis. Survival rate analysis was performed using Kaplan–Meier method. Qualitative parameters were compared using Pearson's chi-square test. Differences were statistically significant at $p < 0.05$.

Results

Pathology contribution to eGFR in elderly and old patients was 26.3 % (14.9 %;35.7 %) %, increasing along CKD severity (Fig. 1).

Given the concept of the cardiorenal syndrome (where failure of one organ causes impaired function of the other organ), stage 2 CKD patients were not included in the analysis, and negative RPC values are probably associated with hyperfiltration and preserved filtration function at this CKD stage.

Renal pathology contribution to eGFR in elderly and old patients was independent of the age: 23.1 % (17.3 %;36.1 %) and 25.6 % (12.7 %;36.7 %) for man and women, respectively, $p = 0.19$. There were no differences in RPC to eGFR in elderly and old patients: 26.3 % (16.2 %;33.7 %) and 26.4 % (11.0 %;36.7 %), respectively, $p = 0.81$) (relationship between RPC to eGFR and patient age: $r = -0.09$, $p = 0.13$) (Fig. 2).

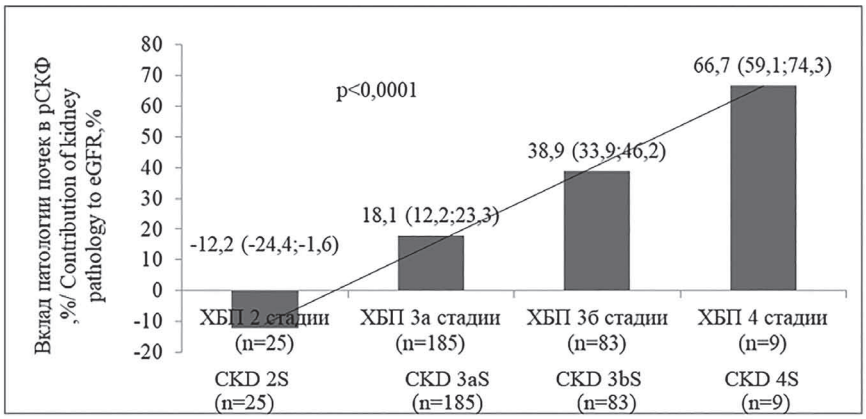

Figure 1. *Contribution of kidney pathology to eGFR in elderly and senile patients depending on the stage of CKD*
Notes eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease

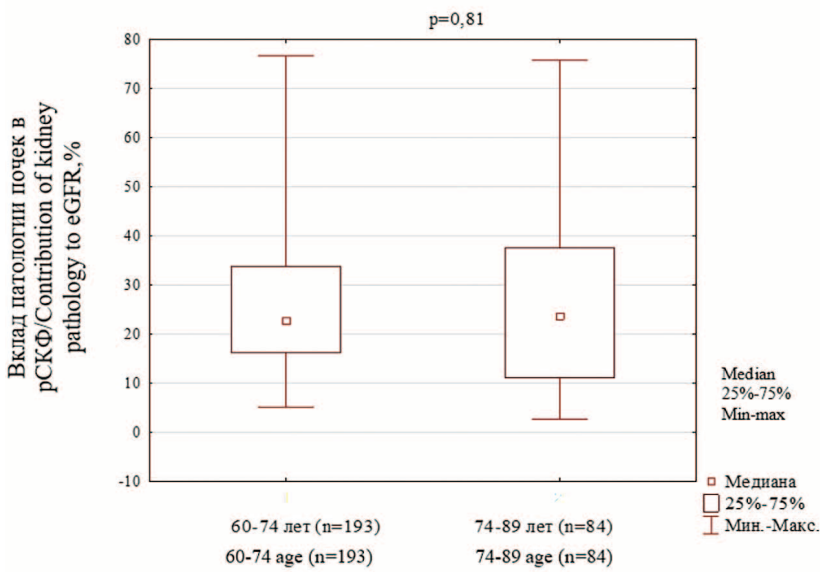

Figure 2. *Contribution of kidney pathology to eGFR in elderly and senile patients depending on age group*
Notes eGFR — estimated glomerular filtration rate

Out of 472 elderly and old patients with stable cardiovascular pathology, prognosis was assessed in 405 patients (85.8 %). During the follow-up period, 47 elderly and old patients (11.6 %) with a stable cardiovascular pathology (38 patients with CKD and 9 patients without CKD) died. Given the lack of the data on the cause of death in a number of patients, cardiovascular mortality was no analysed.

The logistic regression analysis established that the presence of CKD with eGFR of less than 60 mL/min/1.73 m² in elderly and old patients with cardiovascular pathologies is associated with a considerable risk of one-year mortality (OR 2.37; 95 % CI 1.11–5.09; p = 0.017).

Assessment of the prognostic value of RPC to eGFR in elderly and old patients with a stable cardiovascular pathology with or without CKD demonstrated that an increase in RPC to eGFR of over 17.9 % is associated with one-year mortality in elderly and old patients with stable a cardiovascular pathology (OR 2.47; 95 % CI 1.31–4.67; p = 0.004) (Fig. 3).

Renal pathology contribution to estimated GFR of over 43.3 % was associated with a risk of one-year mortality in elderly and old patients with CKD with eGFR of less than 60 mL/min/1.73 m² (OR 4.7; 95 % CI 1.99–10.9; p < 0.0001). Patient survival analysis is presented in Figure 4.

An increase in RPC to eGFR of over 43.3 % was associated with anaemia (OR 2.81; 95 % CI 1.28–6.17; p = 0.009), a history of acute cerebrovascular event

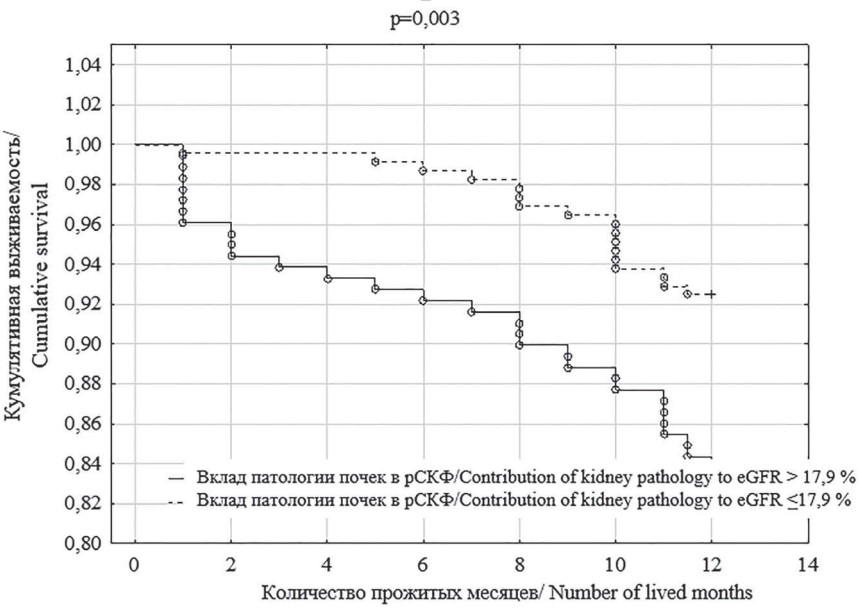

Figure 3. *Cumulative survival of elderly and senile patients with stable cardiovascular pathology depending on the contribution of kidney pathology to eGFR*

Notes. eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease

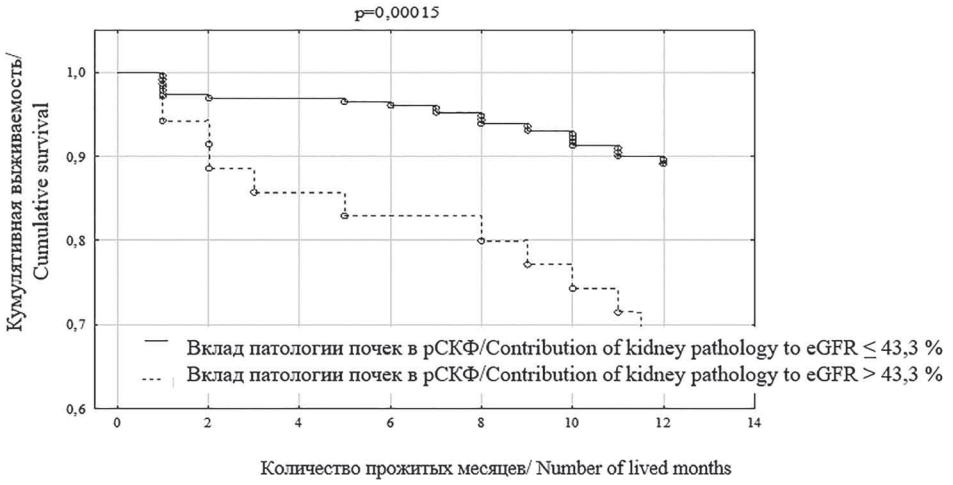

Figure 4. *Cumulative survival of elderly and senile patients with CKD with eGFR less than 60 ml/min/1.73 m² depending on the contribution of kidney pathology to eGFR*

Notes. eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease

(OR 2.82; 95 % CI 1.19–6.66; p = 0.02), atrial fibrillation (OR 2.37; 95 % CI 1.07–5.28; p = 0.03) (Table 2).

Modified Charlson comorbidity index was higher in patients with CKD with RPC to eGFR of over 43.3 % vs. patients with RPC to eGFR of less than 43.3 %: 8 (6;9) and 7 (6;8), respectively, p = 0.004.

Clinical and laboratory values in elderly and old patients with a stable cardiovascular pathology and CKD, depending on RPC to eGFR, are presented in Table 3.

Elderly and old patients with CKD with RPC to eGFR of over 43.3 % had higher body mass index as compared with patients with RPC to eGFR of less than 43.3 % (p = 0.02). Also, it is worth mentioning that elderly and old patients with CKD and RPC of over 43.3 % had higher WBC count (p = 0.005), neutrophils count (p = 0.003) and neutrophil/lymphocyte ratio (p = 0.008). Besides, in patients with CKD and RPC to eGFR of over 43.3 %, serum potassium was higher than in patients with CKD and lower RPC to eGFR: 4.9 (4.4;5.7) and 4.5 (4.1;4.9) mmol/L, respectively, p = 0.004.

Table 2. *Relationship between the contribution of kidney pathology to eGFR more than 43.3 % and comorbidity in patients with CKD with eGFR less than 60 ml/min/1.73 m²*

Comorbidity parameters	OR	95 % CI	p
Diabetes	1,29	0,59–2,79	0,51
Metabolic syndrome	1,1	0,51–2,42	0,79
Obesity	1,81	0,89–3,68	0,09
Coronary artery disease	1,35	0,6–3,04	0,46
History of myocardial infarction	1,02	0,49–2,15	0,95
CHF	0,74	0,15–3,55	0,70
History of stroke	2,82	1,19–6,66	0,02
Anemia	2,81	1,28–6,17	0,009
Atrial fibrillation	2,37	1,07–5,28	0,03

Notes. CI — confidence interval, ACVA — acute cerebrovascular accident, OR — odds ratio, eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease, CHF — chronic heart failure

Table 3. *Clinical and laboratory parameters of elderly and senile patients with CKD with eGFR less than 60 ml/min/1.73 m2 depending on the contribution of kidney pathology in eGFR*

Parameters Me(IQR)	Patients with a contribution of kidney pathology to eGFR of more than 43.3 % (n=36)	Patients with a contribution of kidney pathology to eGFR of less than 43.3 % (n=241)	p
Body mass index, kg/m²	30,4 (27;37,9)	29,0 (25,9;32,7)	0,02
Body fat mass index, kg/m²	11,1 (9,4;17,4)	10,2 (7,9;12,9)	0,02
6-minute walk test, m	305,5 (295;350)	302,5 (290;380)	0,53
SBP, mmHg	130 (130;142,5)	135(139;144)	0,66
DBP, mm Hg.	80 (80;90)	80 (80;90)	0,95
Heart rate, beats per minute	76 (71;84)	72,5 (66;83,5)	0,19
Hemoglobin, g/l	122,5(112;148)	135(121;148)	0,08
Red blood cells, 10^{12}/л	4,5 (3,9;4,9)	4,5 (4;4,8)	0,82
Leukocytes*10^9/л	8,4 (6,4;11,8)	6,8 (5,5;8,2)	0,005
Neutrophils, *109/l	5,7 (4,4;8,4)	4,1 (3,3;5,3)	0,003
Lymphocytes, *10^9/l	1,7 (1,4;2,2)	1,8 (1,4;2,2)	0,72
Monocytes, *10^9/л	0,4 (0,3;0,6)	0,4 (0,2;0,6)	0,77
Eosinophils, *10^9/л	0,09 (0;0,22)	0,07 (0;0,15)	0,59
N/L ratio	3,2 (2,3;5,3)	2,3 (1,7;3,4)	0,008
Eo/Leu ratio	0,03 (0;0,22)	0,02 (0,01;0,07)	0,24
M/L ratio	0,29 (0,17;0,4)	0,24 (0,15;0,35)	0,46
Platelets, * 10^9/л	224 (178;269)	219 (189;268)	0,68
ESR, mm/h	18,5 (11;36,5)	12 (6;22)	0,01
Blood glucose, mmol/l	6,3 (5,4;6,9)	5,9 (5,2;7)	0,56
Total protein, g/l /Total cholesterol, mmol/l	68,4(62,8;71;6)	69,8(64,7;74;4)	0,08
Total cholesterol, mmol/l /	4,7(3,6;5,7)	4,9(3,9;5,8)	0,05
Triglycerides, mmol/l	1,34(0,95;1,49)	1,19(0,87;1,78)	0,82
Sodium, mmol/l	140,5 (137;143,5)	142 (139;144)	0,15
Potassium, mmol/l	4,9 (4,4;5,7)	4,5 (4,1;4,9)	0,004
Fibrinogen, g/l	3,5 (3;4,8)	3,3 (2,7;4,0)	0,16

Notes. DBP — diastolic blood pressure, BMI — body fat mass, SBP — systolic blood pressure, ESR — erythrocyte sedimentation rate, eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease, HR — heart rate. N/L ratio — ratio of neutrophils to lymphocytes, Eo/Leu ratio — ratio of eosinophils to leukocytes, M/L ratio — ratio of monocytes to lymphocytes

Discussion

Renal function impairment with ageing is a serious concern: in individuals over 40 years of age, GFR reduces by 1 mL/min/1.73 m^2 [4, 14]. Age-related reduction in GFR is caused by glomerular sclerosis, tubular atrophy, reduced cortex activity and smaller kidney size [15-17]. Age-related changes in tubular function result in impaired sodium reabsorption, with it being a risk factor for rapid dehydration in elderly people; reduced potassium excretion causing, together with medications, hyperkalaemia; impaired concentration capacity of kidneys, which leads to nocturnal enuresis [18].

In elderly patients, reduced renal function is associated with almost two-fold increase in the incidence of arterial hypertension, ischemic heart disease and cardiac failure [19]. In addition to eGFR assessment, it is essential to take into account the gerontological status of elderly patients (frailty, cognitive disorders, self-care ability) and their comorbidities [20, 21].

The use of calculation formulas for GFR assessment in elderly people with CKD has a number of limitations. The MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formulas are highly accurate, but they underestimate CKD severity in this cohort [22]. The use of the Cockcroft-Gault equation in elderly people is also inaccurate, mostly because the equation uses body weight in calculations: elderly people have less lean body mass due to comorbidities, frailty and malnutrition. In validation of calculation formulas, the number of elderly people over 70 years of age was insufficient. For instance, for the MDRD formula, the mean age in the population was 50.6 ± 12.7 years old, for the Cockcroft-Gault equation, the percentage of patients over 70 years of age was just 23 % [23, 24]. Also, it is worth mentioning that among elderly and old people with CKD there are a lot of patients with diabetes mellitus, who experience hyperfiltration even at early stages of diabetic nephropathy [25].

Given the complexity and ambiguousness of the approach used for elderly and old patients with CKD, the European Renal Association–European Dialysis Transplantation Association (ERA-EDTA) and the European Union Geriatric Medicine Society (EUGMS) developed Clinical Guidelines for the management of elderly patients with stage 3b+ chronic kidney disease [26]. The CKD-EPIcr-cys equation is proposed to be used as the most optimal alternative to direct measurement of the renal function in elderly people (2C is a low-quality recommendation with a low level of evidence) [26].

Therefore, it is recommended to use CKD-EPIcr-cys both for the screening of elderly patients and development of a treatment approach. However, in this case, it is still unclear how a renal pathology contributes to estimated glomerular filtration rate. The proposed method for the determination of RPC is better in forecasting the risk of mortality in elderly people with CKD and a cardiovascular comorbidity.

Conclusion

Renal pathology contribution to estimated GFR in elderly and old patients with CKD and a cardiovascular comorbidity grows along with CKD severity and is independent of sex and age. In elderly and old patients with a stable cardiovascular pathology, renal pathology contribution to estimated GFR of over 17.9 % has prognostic significance in the assessment of one-year mortality vs. eGFR calculation using the CKD EPI formula (as modified in 2011) (OR 2.47; 95 % CI 1.31–4.67; p = 0.004).

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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DOI: 10.20514/2226-6704-2024-14-2-124-131
УДК 616.36-002.2-085.281.8
EDN: PYHQXH

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ЭФФЕКТИВНОСТЬ ПРОТИВОВИРУСНОЙ ТЕРАПИИ АНАЛОГАМИ НУКЛЕОЗ(Т)ИДОВ И ЕЕ ПРЕДИКТОРЫ У ПАЦИЕНТОВ С ХРОНИЧЕСКИМ ГЕПАТИТОМ В

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Efficacy and its Predictors of Antiviral Therapy with Nucleos(T)Ide Analogs in Patients with Chronic Hepatitis B

Резюме

Актуальность. Противовирусная терапия аналогами нуклеоз(т)идов хронического гепатита В направлена на предотвращение прогрессирования заболевания и развития осложнений. Однако существующая терапия не позволяет ликвидировать вирус гепатита В, и для сохранения клинического эффекта у большинства пациентов требуется длительное лечение. В связи с этим изучение факторов, ассоциированных с эффективностью аналогов нуклеоз(т)идов, является актуальным. **Цель** — оценка эффективности и выявление предикторов ответа на противовирусную терапию аналогами нуклеоз(т)идов у пациентов с хроническим гепатитом В. **Материалы и методы.** Ретроспективно-проспективное обсервационное исследование включало 71 пациента с хроническим гепатитом В, получавших аналоги нуклеоз(т)идов в Центре диагностики и лечения хронических вирусных гепатитов в период с 2008 г. по 2023 г. Эффективность терапии аналогами нуклеоз(т)идов оценивалась через 24, 48 и 96 недель приема препаратов. Были изучены прогностические факторы, ассоциированные с получением вирусологического ответа через год противовирусной терапии и с достижением выраженного снижения плотности печени при транзиентной эластометрии. **Результаты.** Частота вирусологического и биохимического ответа увеличивалась по мере продолжения противовирусной терапии, а через 96 недель приема аналогов нуклеоз(т)идов составила 92,6 %. Исходный уровень вирусной нагрузки представляет собой независимый прогностический фактор достижения авиремии через 48 недель терапии (p=0,022). Клиренс HBsAg наблюдался у 2 (2,8 %) пациентов, клиренс HBeAg — у 5 HBeAg-позитивных пациентов. На фоне приема аналогов нуклеоз(т)идов было отмечено значимое снижение фиброза печени по данным транзиентной эластометрии, при этом ее высокий уровень в начале противовирусной терапии является фактором, связанным с выраженным снижением плотности печени (на 25 % и более) (p=0,022). **Заключение.** Противовирусная терапия аналогами нуклеоз(т)идов продемонстрировала высокую эффективность при подавлении репликации вируса гепатита В, нормализации активности аминотрансфераз и уменьшении фиброза печени. Исходные уровни вирусной нагрузки и транзиентной эластометрии являются наиболее важными прогностическими факторами, ассоциированными с эффективностью противовирусной терапии аналогами нуклеоз(т)идов.

Ключевые слова: *противовирусная терапия, аналоги нуклеоз(т)идов, эффективность, фиброз печени*

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Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 02.02.2024 г.
Принята к публикации 14.03.2024 г.

Для цитирования: Нгуен Т.Х., Ильченко Л.Ю., Мельникова Л.И. и др. ЭФФЕКТИВНОСТЬ ПРОТИВОВИРУСНОЙ ТЕРАПИИ АНАЛОГАМИ НУКЛЕОЗ(Т)ИДОВ И ЕЕ ПРЕДИКТОРЫ У ПАЦИЕНТОВ С ХРОНИЧЕСКИМ ГЕПАТИТОМ В. Архивъ внутренней медицины. 2024; 14(2): 124-131. DOI: 10.20514/2226-6704-2024-14-2-124-131. EDN: PYHQXH

Abstract

Background: Antiviral therapy with nucleos(t)ide analogs for chronic hepatitis B is aimed at preventing disease progression and the development of complications. However, current therapies do not allow elimination of hepatitis B virus, and long-term treatment is required to maintain clinical effect in most patients. In this regard, the study of associated factors with the efficacy of antiviral therapy of nucleos(t)ide analogs is actual. **Aim:** To evaluate efficacy and identify predictors of response to antiviral therapy with nucleos(t)ide analogs in patients with chronic hepatitis B. **Materials and methods:** This retrospective-prospective observational study included 71 patients with chronic hepatitis B who received nucleos(t)ide analogs at the Center for Diagnosis and Treatment of Chronic Viral Hepatitis from 2008 to 2023. The efficacy of antiviral therapy with nucleos(t)ide analogs was evaluated after 24, 48, and 96 weeks of drug intake. The prognostic factors associated with obtaining a virologic response after one year of antiviral therapy and with achieving a significant decrease in liver density by transient elastometry were examined. **Results:** The virologic and biochemical response rate increased as antiviral therapy continued, and after 96 weeks of taking nucleos(t)ide analogs was 92.6 %. Baseline viral load level was an independent prognostic factor for achieving aviremia after 48 weeks of antiviral therapy (p=0.022). HBsAg clearance was observed in 2 (2.8 %) patients, HBeAg clearance — in 5 HBeAg-positive patients. On nucleos(t)ide analogs treatment there was a significant decrease of liver fibrosis measured by transient elastometry, and a high level of transient elastometry at the beginning of antiviral therapy is a factor associated with a significant decrease in liver density (by 25 % or more) (p=0.022). **Conclusion:** Antiviral therapy with nucleos(t)ide analogs has demonstrated high efficacy in suppressing hepatitis B virus replication, normalizing aminotransferase activity, and reducing liver fibrosis. Baseline viral load and transient elastometry levels are the most important prognostic factors associated with the efficacy of antiviral therapy with nucleos(t)ide analogs.

Key words: *Antiviral therapy, nucleoside and nucleotide analogs, efficacy, liver fibrosis*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 02.02.2024
Accepted for publication on 14.03.2024

For citation: Nguyen T.H., Ilchenko L.Yu., Melnikova L.I. et al. Efficacy and its Predictors of Antiviral Therapy with Nucleos(T)Ide Analogs in Patients with Chronic Hepatitis B. The Russian Archives of Internal Medicine. 2024; 14(2): 124-131. DOI: 10.20514/2226-6704-2024-14-2-124-131. EDN: PYHQXH

ALT — alanine aminotransferase, NA — nucleoside analogues, AST — aspartate aminotransferase, HBV — hepatitis B virus, VR — virological response, MLDR — marked liver density reduction, DNA — deoxyribonucleic acid, LAM — lamivudine, AVT — antiviral therapy, TBV — telbivudine, TDF — tenofovir disoproxil fumarate, TE — transient elastometry, HF — hepatic fibrosis, CHB — chronic hepatitis B, ETV — entecavir

Introduction

Despite the availability of an efficient hepatitis B virus (HBV) vaccine, chronic hepatitis B (CHB) remains a serious global healthcare concern. According to the World Health Organisation, approximately 300 million people suffer from CHB all over the globe and are at risk of severe hepatic complications [1]. Every year, almost 1 million people all over the world die of hepatic cirrhosis and hepatocellular carcinoma [2]. According to an analysis presented by the Russian Agency for Health and Consumer Rights in 2022, the incidence of CHB in the Russian Federation was 6.37 cases per 100,000 people (9,297 cases), i.e. the rate has increased by 42.5 % vs 2021 [3].

Currently, complete recovery from HBV infections is still impossible because the virus DNA integrates with the host genome, and products which can block or destroy covalently closed circular HBV DNA are at preclinical or early clinical development stage. The key objective of the therapy in patients with CHB is extension of their life expectancy and improvement of the quality of life by preventing disease progression [4].

According to clinical guidelines, nucleoside analogues (NA) are the first-line drugs for antiviral therapy (AVT) in patients with CHB due to their high antiviral activity and safety [4-6]. However, with the use of NAs, the rate of aviremia achievement and fibrosis severity vary. Incomplete virological response (VR), which depends on blood HBV DNA after 12 months of therapy, is observed in 10–30 % of patients who underwent NA therapy [4, 7]. This problem can cause poor compliance among patients.

Therefore, **the objective** of this study is to assess the efficacy of antiviral therapy with NAs and to identify predictors of therapy response in patients with CHB.

Materials and Methods

A retrospective-prospective, observational study included 71 patients with CHB, who were treated with NAs at the Centre for Diagnostics and Therapy of Chronic Viral Hepatitis in 2008–2023.

Inclusion criteria:

1. Patients with CHB
2. Over 18 years of age, both males and females
3. Antiviral therapy with NAs.

Exclusion criteria:

1. Patients with markers of HIV, hepatitis C, hepatitis D
2. Pregnancy and breastfeeding.

Patients were treated with the following NA products: 50 (70.4 %) — entecavir (ETV), 13 (18.3 %) — telbivudine (TBV), 5 (7.0 %) — tenofovir disoproxil fumarate (TDF), 3 (4.2 %) — lamivudine (LAM). The therapy lasted for 6 to 192 months, mean value: 15.0 [12.0–31.0] months.

The efficacy of NA AVT was assessed on the basis of the following:

- Virological response (HBV DNA < 50 IU/mL)
- Biochemical response (alanine aminotransferase (ALT) level of ≤ 40 U/L)
- Serological response (HBsAg clearance/seroconversion, HBeAg clearance/seroconversion in HBeAg-positive patients)
- Reduction in fibrosis severity.

Changes in hepatic fibrosis (HF) during AVT were assessed by transient elastometry (TE) using Fibroscan® (model 502 Touch Echosens, France) in accordance with the standard operating procedures. Marked liver density reduction (MLDR) means reduction in TE value by at least 25 % from the baseline.

Statistical processing was performed using SPSS software (version 25.0; SPSS Inc., USA). Categorial clinical data between independent groups were compared using chi-square and Fischer's exact test, while numerical information was compared with the help of Mann-Whitney test. Changes in numerical data during the therapy were evaluated with Wilcoxon test; McNemar chi-test was used for categorial data. Event probability (taking into account independent variable values) was calculated using binary logistic regression. Reliability operating characteristics (ROC) were analysed in order to assess the factor efficacy for therapy response forecasting and to calculate sensitivity, specificity, area under ROC curve (AUROC), and optimal threshold value. $p < 0.05$ was statistically significant.

The study was approved by the Local Ethics Committee at the N. I. Pirogov Russian National Research Medical University at the Ministry of Health of Russia (Minutes No. 213 dated 13 December 2021).

Results

The test group included 36 male and 35 female patients. The mean age at baseline was 47.0 [30.0–57.0] years old. The majority of patients (81.7 %) were HBeAg-negative. Baseline characteristics of HBeAg-negative and HBeAg-positive patients are presented in Table 1.

HBeAg-positive patients were younger and had high activity of ALT, aspartate aminotransferase (AST) and HBV DNA, as compared to HBeAg-negative patients.

Table 1. *Comparative baseline characteristics of HBeAg-negative and HBeAg-positive patients treated with nucleos(t)ide analogs*

Parameter	HBeAg-negative n=58	HBeAg-positive n=13	p
Age, years	48,0 [33,0-58,0]	30,0 [27,0-43,0]	**<0,05**
Male, n (%)	28 (48,3)	8 (61,5)	>0,05
Platelets, 10^9/l	227 [183-267]	219 [200-250]	>0,05
HBV DNA, $\log_{10}$ IU/mL	4,0 [3,5-4,8]	7,9 [4,3-8,0]	**<0,05**
Alanine aminotransferase, IU/L	33,5 [18,5-60,0]	60,6 [45,0-90,0]	**<0,05**
Aspartataminotransferase, IU/L	27,4 [20,1-46,5]	53,8 [34,2-70,0]	**<0,05**
Transient elastometry, kPa	6,8 [5,4-10,4]	6,1 [5,4-11,8]	
Fibrosis stage F0-1, n (%)	23 (50,0)	6 (60,0)	
Fibrosis stage F2, n (%)	9 (19,6)	1 (10,0)	>0,05
Fibrosis stage F3, n (%)	8 (17,4)	1 (10,0)	
Fibrosis stage F4, n (%)	6 (13,0)	2 (20,0)	

Notes: data are presented as median [25th-75th percentiles] or number (%); p — significance level (statistically significant differences in bold)

Virological response

After 24, 48, 96 weeks of AVT, the rate of virological response (VR) was 69.0 % (47/71), 87.6 % (57/65) and 92.6 % (25/27), respectively (Fig. 1).

On week 24 of AVT, VR was achieved in 77.6 % (45/78) of HBeAg-negative and 30.8 % (4/13) of HBeAg-positive cases, including after the therapy with ETV, TBV, TDF and LAM — 36/50, 10/13, 0/5 and 3/3 cases, respectively.

After 48 weeks of therapy, aviremia was recorded in 92.7 % (50/54) of HBeAg-negative and 63.6 % (7/11) of HBeAg-positive patients. VR was observed as follows: ETV — 42/46, TBV — 10/12, TDF — 2/4, and LAM — 3/3 patients.

The rate of aviremia on week 96 of AVT was 95.2 % (20/21) of HBeAg-negative patients and 83.3 % (5/6) of HBeAg-positive patients.

It has been shown that the rate of VR after 24 and 48 weeks of NA AVT in HBeAg-positive patients was lower than in HBeAg-negative patients ($p < 0.05$). However, after 96 weeks of therapy, no differences were observed ($p > 0.05$) (Fig. 1).

A linear logistic regression model, which included sex, age, platelet count, baseline HBeAg status, baseline HBV DNA, ALT, AST, TE values, demonstrated that initial HBeAg status ($p = 0.016$, 95 % confidence interval (CI) 0.028–0.690), HBV DNA level ($p = 0.001$, 95 % CI 0.259–0.711) and ALT value ($p = 0.048$, 95 % CI 0.876–1.000) were associated with aviremia on week 48 of AVT. According to multivariance analysis results, only baseline HBV DNA level (odds ratio (OR) = 0.534; 95 % CI 0.312–0.914; $p = 0.022$) is an independent prognostic factor of VR.

An analysis of the ROC curve showed that the baseline HBV DNA at the threshold value of ≤ 5.1 $\log 1_{10}$ (≤ 10^5) IU/mL was a good VR predictor at week 48 of therapy (AUROC = 0.894; 95 % CI 0.804–0.984; $p < 0.001$), with sensitivity of 87.5 % and specificity of 82.5 % (Fig. 2).

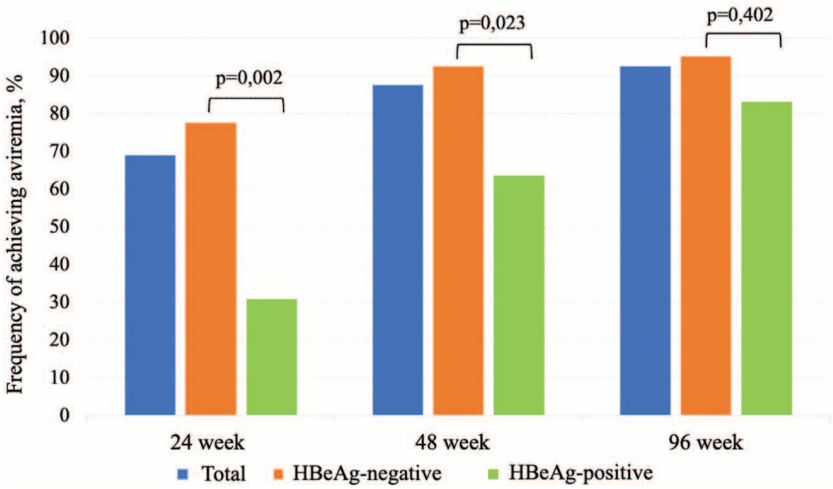

Figure 1. *Frequency of virologic response in HBeAg-negative and HBeAg-positive patients after 24, 48 and 96 weeks of therapy*

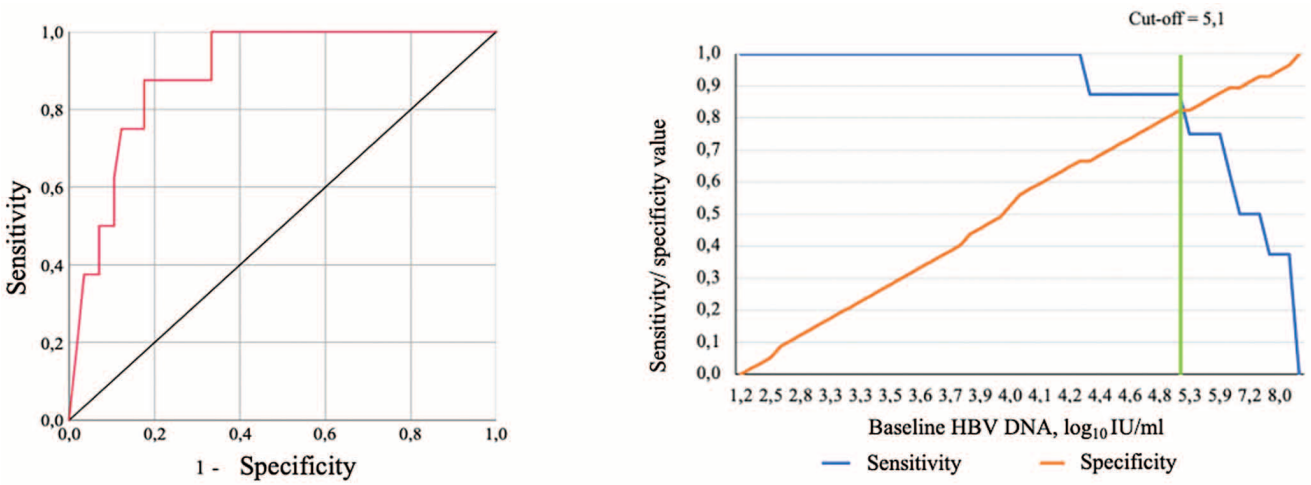

Figure 2. *Baseline HBV DNA level as a predictor of virologic response at week 48 of therapy*

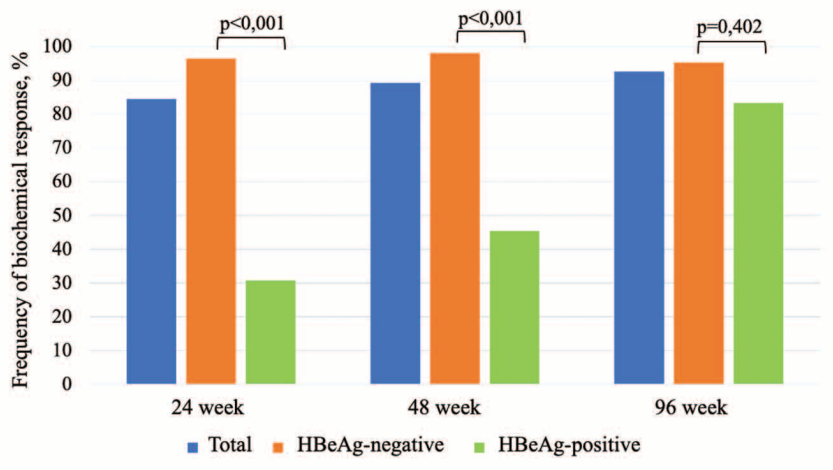

Figure 3. *Frequency of biochemical response in HBeAg-negative and HBeAg-positive patients after 24, 48 and 96 weeks of therapy*

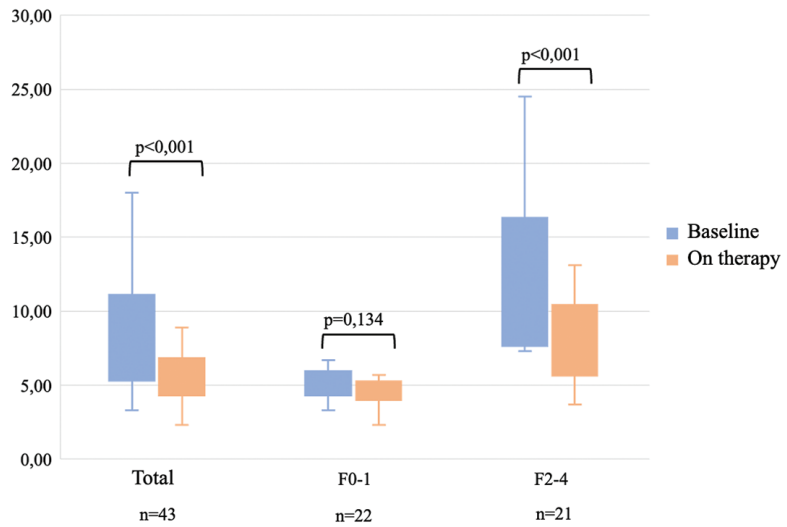

Figure 4. *Dynamics of liver fibrosis during therapy with nucleos(t)ide analogs according to transient elastometry data*

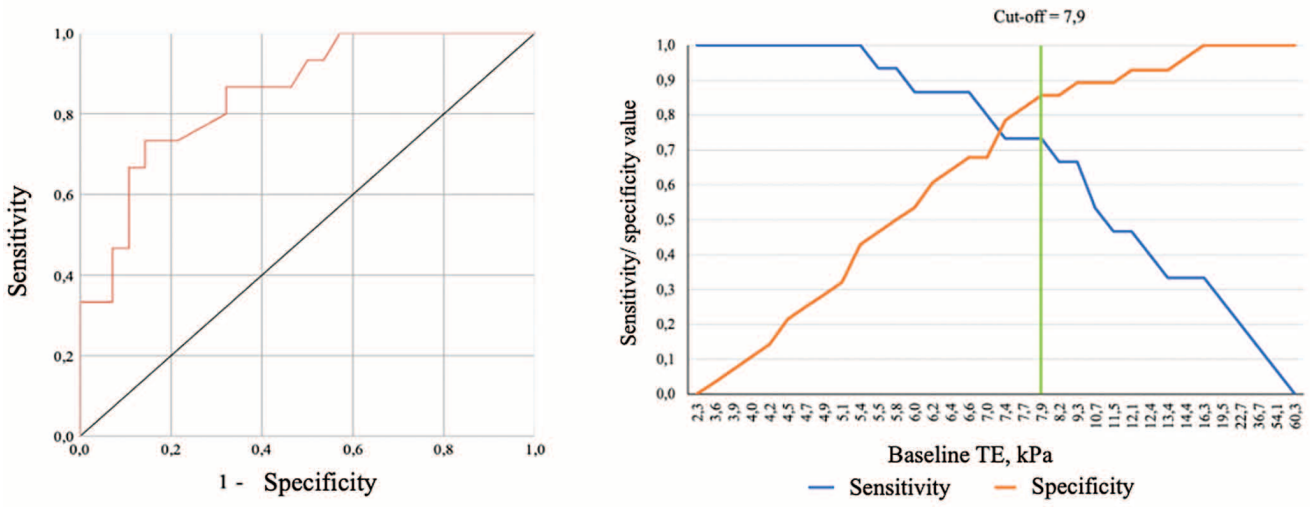

Figure 5. *Baseline level of transient elastometry index as a predictor of achieving a significant decrease in liver density during therapy*

Biochemical response

After24, 48, 96 weeks of AVT, biochemical response was observed in 84.5 % (60/71), 89.2 % (58/65) and 92.6 % (25/27) of cases, respectively (Fig. 3).

On week 24 of therapy, ALT activity normalised in 96.5 % (56/58) of HBeAg-negative and 30.8 % (4/13) of HBeAg-positive patients; on week 48 — in 98.1 % (53/54) and 45.5 % (5/11), respectively; on week 96 — in 95.2 % (20/21) and 83.3 % (5/6), respectively.

It has been demonstrated that, after 24 and 48 weeks of NA AVT, the rate of biochemical response in HBeAg-positive patients was significantly lower than in HBeAg-negative patients ($p < 0.05$); however, after 96 weeks of treatment, no differences were observed ($p > 0.05$) (Fig. 3).

Serological response

Two (2.8 %) patients on ETV had HBsAg claerance. HBsAg seroconversion (anti-HBsAg) was observed in one patient, 27 months after completion of ETV therapy. HBsAg clearance was recorded only in HBeAg-positive patients (2/13).

HBeAg clearance was observed in 5/13 (38.5 %) HBeAg-positive patients, including four patients with HBeAg seroconversion. HBeAg clearance was achieved in three cases of ETV therapy, 1 case of TBV therapy, and one case of TDF therapy.

Changes in hepatic fibrosis

Changes in HF were assessed using TE in 43 cases, with the mean interval between first and repeated procedure of 21.0 [12.0–30.0] months.

According to the METAVIR scale, TE data were used to diagnose stage F0-1 at the beginning of AVT in 22 (51.2 %) patients, F2 — in 8 (18.6 %) patients, F3 — in 6 (14.0 %) patients, and F4 — in 7 (16.3 %) patients.

The therapy resulted in TE value reduction from 6.7 [5.3–11.1] kPa to 5.3 [4.3–6.8] kPa ($p < 0.001$), and in patients with F2-4 this reduction was statistically significant (from 11.1 [7.8–14.6] kPa to 6.8 [6.0–8.9] kPa ($p < 0.001$)) (Fig. 4).

HF regression by at least 1 point was observed in 55.8 % of cases. After AVT, a share of patients with HF stage F0-1 increased from 51.2 % to 76.7 %. The majority (72.1 %) of patients demonstrated reduction in TE values by at least 10 %, and MLDR (by at least 25 %) was achieved in 15 (34.9 %) cases.

According to linear logistic regression results, MLDR-associated factors were age ($p = 0.027$, 95 % CI 1.006–1.102), sex ($p = 0.048$, 95 % CI 1.028–13.515) and TE at the beginning of AVT ($p = 0.008$, 95 % CI 1.086–1.710). A multivariance analysis demonstrated that the baseline TE level (OR = 1.345; 95 % CI 1.044–1.732; $p = 0.022$) should be treated as an independent prognostic factor of MLDR achievement.

ROC curve analysis showed the TE value at the beginning of AVT with the threshold value of ≥ 7.9 kPa as a predictor of MLDR (AUROC = 0.851; $p < 0.001$), where sensitivity is 73.3 % and specificity is 85.7 % (Fig. 5).

Discussion

Currently, NAs are recommended as a first-line therapy for patients with chronic HBV infection due to its high efficacy in inhibition of virus replication and prevention of disease progression [4-6].

This study has demonstrated higher rates of achieving non-detectable HBV DNA levels and ALT activity normalisation with continued NA AVT. In their work, J.-Y. Cho et al. reported anaemia in 80.0 %, 95.6 % and 99.4 % of patients during year 1, 3 and 5 of ETV therapy, respectively [8]. F. Suzuki et al. observed virological response in 81 %, 89 % and 91 % of patients undergoing ETV therapy after 1, 2 and 3 years, respectively [9].

Our data demonstrated that the rate of virological and biochemical response after 24, 48 weeks of treatment was significantly lower in HBeAg-positive patients as compared with HBeAg-negative patients. However, after 96 weeks of therapy, there were no statistically significant differences. This result can be explained by higher levels of HBV DNA and transaminases at the beginning of AVT in HBeAg-positive patients vs. HBeAg-negative patients. Rapid achievement of aviremia and ALT activity normalisation in HBeAg-negative patients was also described in a paper by Ibragimov EK et al. [10] and in a paper by Jacobson IM et al. [11].

In this study, HBV DNA at the beginning of AVT of > 10^5 IU/mL was an independent predictor of delayed virological response during the first year of therapy. Similar data on delayed aviremia in patients with a high baseline HBV DNA level were obtained by H. Zhou et al. [12].

Earlier studies demonstrated that reduction in TE values correlates with less severe HF [13, 14]. W. Xu et al. showed that reduction in TE values by 25 % and more is optimal for forecasting HP regression based on liver biopsy results [14].

AVT resulted in reduction in HF severity (according to TE), and a significant drop in the TE value was observed in patients with F2-F4. The share of patients with stage F0/F1 increased from 51.2 % to 76.7 %.

MLDR (reduction in TE by ≥ 25 %) was observed in 34.9 % of patients receiving NAs. ROC curve analysis demonstrated that the baseline TE at the threshold value of ≥ 7.9 kPa is a good predictor of MLDR, with sensitivity of 73.3 % and specificity of 85.7 %. The obtained results allowed seeing that the efficacy of NA AVT was higher in patients with marked fibrosis in comparison to minor fibrosis, thus pointing out

to the significance of AVT in hepatic cirrhosis and marked fibrosis [15].

Conclusions

NAs are efficient in inhibiting virus replication; they normalise functional status of the liver and reduce HF severity. Low HBV DNA levels at the beginning of AVT are an independent prognostic factor of aviremia achievement during the first year of the therapy. The use of TE in clinical practice makes it possible to efficiently monitor changes in HF during the treatment with NA AVT in patients with CHB.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2024-14-2-132-143
УДК 616.24-002-036.88-074/-076
EDN: XXAFUZ

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РАННИЕ КЛИНИКО-ЛАБОРАТОРНЫЕ ПРЕДИКТОРЫ ГОСПИТАЛЬНОЙ ЛЕТАЛЬНОСТИ У ПАЦИЕНТОВ С СЕПСИСОМ НА ФОНЕ ПНЕВМОНИИ

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Early Clinical and Laboratory Predictors of Hospital Mortality in Patients with Sepsis Secondary to Pneumonia

Абстракт

Несмотря на значительный прогресс в области профилактики, ранней диагностики и антибактериальной терапии, внебольничная пневмония по-прежнему сохраняет статус не только наиболее распространенного среди острых инфекционных заболеваний, но и является частым источником развития сепсиса, многократно повышающего вероятность летального исхода в данной группе пациентов. **Целью исследования** стало выполнение сравнительного анализа клинико-лабораторных показателей и оценка характера их изменений в первые 48 часов от момента верификации сепсиса, развившегося на фоне пневмонии, у пациентов терапевтического отделения в зависимости от исхода госпитализации. **Клинические группы и методы исследования.** Выполнено ретроспективное сравнительное исследование, включившее методом сплошной выборки пациентов с сепсисом, развившемся на фоне пневмонии у пациентов, госпитализированных в терапевтические клиники ФГБОУ ВО СибГМУ Минздрава России в период с 01.01.2019 г. по 30.04.2023 г. Всего в исследование включены 40 пациентов обоего пола с последующим разделением на две группы сравнения в зависимости от исхода госпитализации (выписка из стационара или наступление летального исхода) для динамической оценки клинико-анамнестических и лабораторных параметров в ранние сроки развития септического состояния (первые 48 часов) с целью определения их связи с исходом госпитализации. **Результаты.** Все пациенты были разделены на 2 группы. Первую группу (n=17, 42,5 %) составили пациенты с благоприятным исходом госпитализации (выздоровление), вторую группу (n=23, 57,5 %) составили пациенты с летальным исходом. На момент верификации сепсиса пациенты с благоприятным исходом имели значимо ниже балл по шкале SOFA (3 (2; 6) балла), чем у пациентов с летальным исходом (6 (5; 7) баллов), p=0,037. Изменение концентрации мочевины в первые 48 часов от момента верификации сепсиса в группе выживших составило -1,3 (-4,4; 1,99) ммоль/л, а в группе умерших 5,5 (-1,5; 12,2) ммоль/л, p=0,020. В группе умерших пациентов 8 человек (34 %) на момент верификации сепсиса имели сочетание гипотонии (<90/60 мм рт. ст.) и содержание лактата в сыворотке крови >5 ммоль/л. В группе выживших гипотония наблюдалась только у 2 человек (11 %), причем показатели уровня лактата у этих пациентов находились в диапазоне 4,5-4,6 ммоль/л. В точке 1 показатели незрелых гранулоцитов статистически значимо не различались у выживших и умерших пациентов (1,2 (0,7; 2,1)% vs 0,8 (0,6; 1,5)%, соответственно, p>0,05). Через 48 часов уровень незрелых гранулоцитов нарастал у выживших паци-

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ентов до 1,5 (1; 3,2)% и наоборот, снижался до 0,65 (0,45; 1,45)% в группе умерших, причем разница этих показателей между группами стала статистически значимой, p <0,05. **Заключение.** У пациентов с сепсисом на фоне тяжелой пневмонии летальность составила 57,5 %. С целью выделения групп высокого риска летального исхода помимо оценки по шкале SOFA следует осуществлять динамический контроль в первые 48 часов от момента верификации септического состояния таких биомаркеров, как уровень мочевины, лактата, уровень незрелых гранулоцитов и ретикулоцитов.

Ключевые слова: *сепсис, летальность, пневмония, предикторы летального исхода*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 19.12.2023 г.
Принята к публикации 12.03.2024 г.

Для цитирования: Родионова Ю.О., Старовойтова Е.А., Федосенко С.В. и др. РАННИЕ КЛИНИКО-ЛАБОРАТОРНЫЕ ПРЕДИКТОРЫ ГОСПИТАЛЬНОЙ ЛЕТАЛЬНОСТИ У ПАЦИЕНТОВ С СЕПСИСОМ НА ФОНЕ ПНЕВМОНИИ. Архивъ внутренней медицины. 2024; 14(2): 132-143. DOI: 10.20514/2226-6704-2024-14-2-132-143. EDN: XXAFUZ

Abstract

Despite significant progress in the field of prevention, early diagnosis and antibacterial therapy, community-acquired pneumonia still retains the status of not only the most common among acute infectious diseases, but is also a frequent source of sepsis, which greatly increases the likelihood of death in this group of patients. The purpose of the study was to perform a comparative analysis of clinical and laboratory parameters and assess the nature of their changes in the first 48 hours from the moment of verification of sepsis that developed against the background of pneumonia in patients of the therapeutic department, depending on the outcome of hospitalization. **Clinical groups and research methods.** A retrospective comparative study was carried out, which included, using a continuous sampling method, patients with sepsis that developed against the background of pneumonia in patients hospitalized in therapeutic clinics of the Federal State Budgetary Educational Institution of Higher Education Siberian State Medical University of the Ministry of Health of Russia in the period from 01/01/2019 to 04/30/2023. In total, the study included 40 patients of both gender, followed by division into two comparison groups depending on the outcome of hospitalization (discharge from hospital or death) for the dynamic assessment of clinical, anamnestic and laboratory parameters in the early stages of the development of a septic condition (the first 48 hours) in order to determine their relationship with the outcome of hospitalization. **Results.** All patients were divided into 2 groups. The first group (n=17, 42.5 %) consisted of patients with a favorable outcome of hospitalization (recovery), the second group (n=23, 57.5 %) consisted of patients with a fatal outcome. At the time of verification of sepsis, patients with a favorable outcome had a significantly lower SOFA score (3 (2; 6) points) than patients with a fatal outcome (6 (5; 7) points), p = 0.037. The change in urea concentration in the first 48 hours from the moment of verification of sepsis, which in the group of survivors was -1.3 (-4.4; 1.99) mmol/l, and in the group of deceased 5.5 (-1.5; 12. 2) mmol/l, p=0.020. In the group of deceased patients, 8 people (34 %) at the time of verification of sepsis had a combination of hypotension (<90/60 mm Hg) and serum lactate >5 mmol/l. In the survivor group, hypotension was observed in only 2 people (11 %), and lactate levels in these patients were in the range of 4.5-4.6 mmol/l. At point 1, the indicators of immature granulocytes were not statistically significantly different between surviving and deceased patients (1.2 (0.7; 2.1)% vs 0.8 (0.6; 1.5)%, respectively, p>0. 05). After 48 hours, the level of immature granulocytes increased in surviving patients to 1.5 (1; 3.2)% and, conversely, decreased to 0.65 (0.45; 1.45)% in the group of deceased patients, and the difference in these indicators between groups became statistically significant, p <0.05. **Conclusion.** Thus, in patients with sepsis against the background of severe pneumonia, the mortality rate was 57.5 %. In order to identify groups at high risk of death due to sepsis due to pneumonia, in addition to the SOFA scale, dynamic monitoring of biomarkers such as urea, lactate, immature granulocytes and reticulocytes should be carried out in the first 48 hours from the moment of verification of the septic state.

Key words: *sepsis, mortality, pneumonia, predictors of death*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 19.12.2023
Accepted for publication on 12.03.2024

For citation: Rodionova Yu.O., Starovoitova E.A., Fedosenko S.V. et al. Early Clinical and Laboratory Predictors of Hospital Mortality in Patients with Sepsis Secondary to Pneumonia. The Russian Archives of Internal Medicine. 2024; 14(2): 132-143. DOI: 10.20514/2226-6704-2024-14-2-132-143. EDN: XXAFUZ

Introduction

Pneumonia remains the most common acute infectious diseases and, according to the World Health Organization, it takes the fourth place among causes of death globally [1]. In 2109 in the Russian Federation, the incidence of community-acquired pneumonia among adults was 410 per 100,000 people [2]. In 2018 in Russia, pneumonia mortality was 17.0 per 100,000 people [3]. Severe community-acquired pneumonia, which complications include marked acute respiratory failure

and/or sepsis, is of special interest. According to some authors, the need for intensive care in patients hospitalised with community-acquired pneumonia can be as high as 21 % because of organ dysfunction and sepsis [4]. According to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), setting forth new definitions and diagnostic criteria, sepsis is an "acute, life-threatening organ dysfunction, caused by impaired regulation (dysregulation) of host response to infection" [5, 6]. Since clarification of the source of infection is important for sepsis verification, the criteria for pneumonia-associated sepsis should include the presence of an identified site of infection and acute organ dysfunction, confirmed with assessment results of ≥ 2 points under the SOFA (Sequential Organ Failure Assessment).

According to various authors, mortality caused by pneumonia-associated mortality is relatively high and is 41 % to 50 % in various populations [7, 8]. Despite the developed diagnostic scales used in early diagnosis of a septic condition, the search for predictors to identify patients at a high risk of death is ongoing. According to literature, promising prognostic factors can be age, lactate concentration, body temperature, oxygenation index, bilirubin levels, Glasgow coma scale, hepatic disorders, cancer, organ transplantation, troponin T levels, neutrophil-to-lymphocyte ratio (NLR), and use of vasoconstrictors [9]. The main requirement for these parameters is their ability to change over time and the possibility to accurately forecast disease outcome. Currently, the search for such predictors is ongoing; therefore, it is important to assess the early changes in clinical and laboratory parameters in order to evaluate their prognostic value in hospitalised patients with pneumonia-associated sepsis.

Thus, **the objective of this study** is a comparative analysis of clinical and laboratory parameters and assessment of the nature of their changes during the first 48 hours after verification of pneumonia-associated sepsis in patients, depending on hospitalisation outcome.

Clinical Groups and Study Methods

The study protocol approved by the Local Ethics Committee (LEC) at the Siberian State Medical University of the Ministry of Health of Russia (LEC resolution No. 8616/1 dated 29 March 2021) was used to conduct a retrospective, comparative study of patients with pneumonia-associated sepsis hospitalised to the Clinic of the Siberian State Medical University of the Ministry of Health of Russia during the period from September 1, 2019 to April 20, 2023, who were included in the study under the continuous sampling method. 40 male and female patients were included in the study and divided into two groups, depending on the hospitalisation outcome (discharge or death), for dynamic assessment of their clinical and laboratory parameters at early stages of a septic condition (first 48 hours), in order to establish their relation to hospitalisation outcome.

The study enrolled patients with pneumonia and SOFA score of ≥ 2 points (Sequential Organ Failure Assessment, which includes hypotonia (systolic blood pressure below 100 mm Hg), respiratory distress (respiratory rate at least 22 respirations per minute), as well as altered mental status, assessed using the Glasgow coma scale (< 15 points), where each indicator was assigned 1 point), as well as availability of complete information about the disease and clinical and laboratory parameters, stated in the inpatient medical record and information registration system used by the medical institution.

In this study, the information on the nature, duration and outcome of hospitalisation, anthropometric data (sex, age, height, weight, body mass index (BMI)), presence of comorbidity/underlying pathology (including potential causes and confirmed immunodeficient conditions) were analysed. All patients had their qSOFA and SOFA recorded; also, the following information was documented: duration of the septic condition, information on patient's admission to the intensive care unit (ICU) (duration, artificial pulmonary ventilation, vasoconstrictor support); objective parameters (BP, HR, consciousness, SpO2) were monitored. All patients underwent assessment of the results in accordance with the unified list of laboratory tests during verification (point 1) and 48 hours later (point 2): serum iron, electrolytes, arterial blood gases, C-reactive protein (CRP), lactate, procalcitonin, sodium, potassium, urea, total bilirubin, direct bilirubin, calcium, CBC+DIFF (with calculation of the neutrophil-to-lymphocyte ratio (NLR) and eosinophil count). In this study, we used a differentiated approach to the calculation of reticulocyte count, depending on their maturity, using Sysmex XN-1000 blood analyser (Sysmex, Germany). Reticulocyte measurements were based on the principle of fluorescent flow cytometry with the use of a nucleinic acid colourant oxazine 750, which stains RNA cells. Depending on their maturity, reticulocytes have different fluorescence intensity, thus, they are subdivided into three subtypes: mature reticulocytes with

limited fluorescence are called "low fluorescence reticulocytes" (LFR), intermediately mature reticulocytes are "medium fluorescence reticulocytes" (MFR), while very immature reticulocytes are "high fluorescence reticulocytes" (HFR). Immature reticulocyte fraction (IRF) is the percentage of immature reticulocytes calculated as the sum of MFR and HFR; it represents erythropoietic activity.

Statistical analysis was performed in Statistica 12.0 (IBM SPSS Statistics, USA). Quantitative parameters are described using median (25th; 75th percentiles). Qualitative parameters are described using absolute and relative frequencies, n (%). Quantitative and qualitative parameters in independent samples were compared with the help of Mann–Whitney U test and Pearson's chi-square test or Fisher's exact test. Quantitative parameters in dependent samples were compared using Wilcoxon rank sum test. ROC analysis was performed in MedCalc SW, Version 18.9.1. The area under curve (AUC) with 95 % confidence interval, cutoff point using Youden's index, sensitivity and specificity of this point, were assessed. Results were statistically significant at $p < 0.05$.

Study Results

18 female (45 %) and 22 male (55 %) patients were included in the study. All patients were divided into two groups. Group 1 (n = 17, 42.5 %) were patients with a favourable outcome of hospitalisation (recovery); group 2 (n = 23, 57.5 %) were patients who died. There were no statistically significant differences in age (68 (41; 77) years old and 67 (58; 81) years old, p = 0.373) and BMI (25.45 (20.76; 30.72) and 25.85 (23; 27.68), p = 0.711, respectively) between the groups. In the survivors group, 64.7 % were men and 35.3 % were women, whereas in the other group 47.8 % were men and 52.2 % were women ($p > 0.05$). The most common comorbidities in the group of patients with unfavourable outcome were IHD, hypertensive disease, a history of myocardial infarction, stage 2–3 CHF; however, there were no statistically significant differences in comorbidities between the groups (intergroup p for all conditions was > 0.05) (Table 1).

In this study, in 56 % of patients, sepsis was diagnosed on the first day of hospitalisation. It is interesting to note the trend towards earlier diagnosis of sepsis in the group of patients with lethal outcome (day 1 (1; 4) of hospitalisation) as compared to survivors (day 2 (1; 5) of hospitalisation); however, there were no statistically significant differences, $p > 0.05$.

The qSOFA scale was used as a preliminary sorting tool, because the study enrolled patients with confirmed pneumonia and qSOFA score of ≥ 2 points (Table 2). An analysis of differences using Fisher's exact test demonstrated that, in the group with favourable outcome, 16 (94.12 %) patients had qSOFA score of 2 points and only one patient had a score of 3 points, whereas in the group with lethal outcome, 14 (60.87 %) patients had a score of 2 points and 9 (39.13 %) patients — 3 points (p = 0.018).

At the moment when sepsis was verified on the basis of an assessment of organ dysfunction severity (SOFA), statistically significant differences were observed. At the moment when sepsis was verified, patients with favourable outcome had a significantly lower SOFA score (3 (2; 6) points) as compared to patients who died (6 (5; 7) points), p = 0.037.

Patients who died had spent less time in an inpatient unit because of their unfavourable outcome: 7 (2; 16) days vs 30 (13; 48) days in the group of patients

Table 1. *Presence of concomitant pathology in patients diagnosed with sepsis*

Concomitant pathology	Patients with a favorable outcome, n (%)	Fatal patients, n (%)
Cardiac ischemia	9 (52,9 %)	16 (69,5 %)
Hypertonic disease	10 (58,8 %)	18 (78,7 %)
History of myocardial infarction	3 (17,6 %)	8 (34,7 %)
Chronic heart failure stages 2-3	9 (52,9 %)	12 (52,2 %)
Diabetes mellitus type 2	5 (29,4 %)	5 (21,7 %)
COPD	2 (11,7 %)	3 (13,0 %)
HIV	5 (29,4 %)	2 (8,6 %)
Addiction	5 (29,4 %)	2 (8,6 %)

Note: COPD — chronic obstructive pulmonary disease, HIV — human immunodeficiency virus

Table 2. Clinical characteristics of patients

	1. Patients with a favorable outcome Me (Q1; Q3)	2. Fatal patients Me (Q1; Q3)	P_{1-2}
Number of people, n (%)	17 (42,5 %)	23 (57,5 %)	-
Duration of hospitalization, bed days	30 (13; 48)	7(2; 16)	0,0003
Age, years	68 (41; 77)	67 (58; 81)	0,373
BMI, kg/m^2	25,45 (20,76; 30,72)	25,85 (23; 27,68)	0,711
Number of qSOFA points, point	2 (2; 2)	2 (2; 3)	0,017
Diagnosis of sepsis from the beginning of hospitalization, day	2 (1; 5)	1 (1; 4)	0,678
Duration of hospitalization for sepsis, days	6 (3; 9)	4 (2; 8)	0,236
Assessment of the severity of organ dysfunction according to the SOFA scale, score	3 (2; 6)	6 (5; 7)	0,037
Duration of stay in the ICU, bed days	6 (3; 12)	4 (1; 4)	0,115
Duration of use of vasopressors, days	3,5 (2; 5)	1 (1; 3,5)	0,141
Objective data at the time of diagnosis of septic condition			
Body temperature, °C	38 (37,7; 38,5)	37,8 (36,6; 38)	0,085
Heart rate, beats/min	101 (90; 115)	110 (90; 120)	0,467
NPV, in a minute	25 (24; 28)	26 (24; 30)	0,499
Systolic blood pressure, mm hg art.	100 (97; 120)	100 (90; 120)	0,362
Diastolic blood pressure, mm hg art.	60 (60; 70)	60 (60; 70)	0,156
Pulse blood pressure, mm hg frt.	40 (30; 50)	40 (30; 50)	0,625
SpO_2, %	90 (90; 96)	93 (90; 95)	0,923
Glasgow scale, point	13 (13; 13)	13 (13; 13)	0,086

Note: BMI — body mass index, (q)SOFA — (quick) Sequential Organ Failure Assessment, scale for (quick) assessment of organ failure, ICU — intensive care unit, HR — heart rate per 1 minute, RR — respiratory rate movements per minute, BP — blood pressure, SpO2 — oxygen saturation of peripheral blood

with favourable outcome of sepsis, $p < 0.001$. Duration of ICU admission and number of days on vasoconstrictors and antibiotics in the survivors group were lower in survivors; however, differences were not statistically significant (Table 2). It is worth mentioning that in the survivors group there were only two cases (11.7 %) of artificial pulmonary ventilation and vasoconstrictors, whereas in the other group such interventions were required by 11 patients (47.8 %).

Of note, at the moment when sepsis was diagnosed, such objective parameters as body temperature, HR, RR, arterial and pulse pressure, oxygen saturation and Glasgow coma scale score were not significantly different in the groups of favourable and poor outcomes (Table 2). It proves that it is not possible to forecast disease outcome only on the basis of these parameters.

All patients had their key biochemical and haematological parameters analysed.

Creatinine and Urea As Renal Function Markers

It has been shown that, at the moment when sepsis was verified, 85 % of patients were diagnosed with changes in biochemical parameters, which correspond to kidney injury (increased urea and/or creatinine levels). Urea levels in point 1 were lower in survivors vs. patients who died (10.8 (8.9; 19.8) vs 16.9 (10.7; 28.2) mmol/L; however, there were no statistically significant differences between the groups. Over time (point 2, 48 hours later), urea levels in survivors dropped to 10.4 (5; 19.3) mmol/L (no significant difference vs baseline), whereas in the group of patients with poor outcome, urea rose to 24 (14.8; 32.6) mmol/L (0.020); and 48 hours later, serum urea concentration in this group was considerably higher than in survivors, $p = 0.020$. Changes in urea concentration during the first 48 hours after sepsis verification in survivors was

-1.3 (-4.4; 1.99) mmol/L, while in the other group — 5.5 (-1.5; 12.2) mmol/L, p = 0.020.

A similar pattern was observed for creatinine; however, there were no statistically significant differences between the groups either in point 1 (108 (78; 150) μmol/L vs 139.2 (75.5; 195) μmol/L, respectively, p > 0.05) or in point 2 (48 hours later), despite a trend towards lower creatinine levels in survivors (76 (64; 134) μmol/L) and increased creatinine levels in the other group (148.3 (76; 255) μmol/L).

Lactate As a Marker of Cellular Damage

It is well known that, if serum lactic acid levels rise to the concentration of over 5.0 mmol/L and pH drops below 7.25, metabolic acidosis (lactic acidosis) develops. Lactic acidosis is an acute complication, caused by a sharp increase in blood lactate levels, which can result in death, especially if combined with hypotonia [5]. In this study, baseline lactate levels of over 4.5 mmol/L were recorded in 16 patients (40 %). When blood concentrations of this biomarker were analysed in point 1, it has been shown that in survivors the blood lactic acid levels were considerably lower (3.6 (3.1; 4.5) mmol/L vs the group with poor outcome (5.2 (4; 5.6) mmol/L (p = 0.004). When this parameter was assessed in point 2, there was a common trend towards reduction in both groups; however, there still were statistically significant differences between survivors and those who died (2.75 (2.1; 3.6) mmol/L vs 3.9 (3; 6.5) mmol/L, respectively, p = 0.011).

In the group with poor outcome, at the moment when sepsis was verified, 8 patients (34 %) had hypotonia (< 90/60 mm Hg) and high serum lactate levels (> 5 mmol/L). In survivors, hypotonia was observed only in 2 patients (11 %), with lactate levels being 4.5-4.6 mmol/L.

Blood Count

Recently, literature sources actively describe one parameter of complete blood count — *relative and absolute count of immature granulocytes (IG)*. The term "immature granulocyte" includes promyelocytes, myelocytes, metamyelocytes. Normally, immature granulocyte are not present in peripheral blood and appear only when neoplastic or infectious inflammatory processes begin. Positive correlation of this parameter with WBC and procalcitonin levels in infectious inflammatory processes has been observed [10, 11]. An analysis of relative immature granulocyte count in groups with favourable and poor outcome demonstrated that in point 1 the IG value is not statistically different in both groups (1.2 (0.7; 2.1) % vs 0.8 (0.6; 1.5) %, respectively, p > 0.05). In 48 hours, IG increased in survivors to 1.5 (1; 3.2) %, and vice versa dropped to 0.65 (0.45; 1.45) % in the poor outcome patients, and the difference between groups became statistically significant, p < 0.05. Similar trends were observed for the absolute immature granulocyte count (Table 3). It is important to note that WBC count was higher both at the moment of sepsis verification and after 48 hours in patients with poor outcome of the disease (Table 3).

Reticulocytes. Development of respiratory distress activates compensatory erythropoiesis. The number of immature reticulocytes in peripheral blood represents the erythropoietic activity of the bone marrow. In this study, the relative immature reticulocyte count (IRF%) in point 1 was significantly higher in patients with poor outcome vs survivors (27.5 (16.1; 31.2) % vs 10.9 (7.8; 15.6) %, p = 0.005). In 48 hours, the relative immature reticulocyte count reduced in both groups, but remained high in patients with poor outcome (20.8 (13; 28.7) % vs 7.8 (4.8; 10.1) %), p = 0.024).A similar trend was observed for the relative count of medium reticulocytes (MFR, %) (Table 4).

The relative mature reticulocyte count (LFR, %) was initially higher in patients with favourable outcome (p = 0.004). In point 2, this parameter rose in both groups, and the difference between groups was not statistically significant (Table 4).

In this paper, we conducted ROC analysis of a number of parameters and identified some potential predictors of death.

- Organ dysfunction severity using the SOFA score: AUC 0.692 [95 % CI 0.526; 0.828], p = 0.0281. SOFA > 3 is a factor of poor outcome, where sensitivity and specificity are 82 % and 53 %, respectively.
- Urea levels in point 2 (48 hours after sepsis diagnosis): AUC 0.751 [95 % CI 0.560; 0.890], p = 0.0055. Urea levels of > 14.5 mmol/L are a factor of poor outcome, where sensitivity and specificity are 77 % and 64 %, respectively. Also, an important factor to predict poor outcome is an increase in urea values of > 2.5 mmol/L during the first 48 hours after sepsis diagnosis: AUC 0.751 [95 % CI 0.560; 0.890], p = 0.0072, where sensitivity and specificity are 61 % and 88 %, respectively.
- Lactate levels upon diagnosis (point 1) and in 48 hours (point 2). Lactate levels of > 4.6 mmol/L

in point 1 (AUC 0.810 [95 % CI 0.621; 0.931], p = 0.0003, sensitivity 67 %, specificity 93 %) and lactate levels of > 3.7 mmol/L in point 2 (AUC 0.799 [95 % CI 0.591; 0.931], p = 0.0013, sensitivity 63 %, specificity 86 %) can be prognostic of poor outcome.

- Relative count of immature granulocytes in point 2 (48 hours after sepsis diagnosis) of ≤ 0.9 %: AUC 0.762 [95 % CI 0.556; 0.905], p = 0.0151, sensitivity 75 %, specificity 86 %.
- Absolute count of immature granulocytes in point 2 (48 hours after sepsis diagnosis) of ≤ 0.11*10^9/L: AUC 0.735 [95 % CI 0.527; 0.887], p = 0.0233, sensitivity 66 %, specificity 78 %.
- Absolute reticulocyte count (RET#) in point 2 of > 46.3*10^9/L is a predictor of death: AUC 0.800 [95 % CI 0.539; 0.951], p = 0.0157, sensitivity 80 %, specificity 85 %.
- Relative immature reticulocyte count (IRF, %): a level of > 12.2 % in point 1 (AUC 0.855 [95 % CI 0.640; 0.967], p = 0.0001, sensitivity 100 %, specificity 67 %) and > 10.1 % in point 2 (AUC 0.829 [95 % CI 0.571; 0.964], p = 0.0032, sensitivity 80 %, specificity 85 %) is a predictor.

Table 3. *Biochemical parameters in patients with favorable and unfavorable outcomes*

Index	1. Patients with a favorable outcome Me (Q1; Q3)	2. Fatal patients Me (Q1; Q3)	p_{1-2}
Urea, mmol/l, initially	n=17 10,8 (8,9; 19,8)	n=23 16,9 (10,7; 28,2)	0,077
Urea, mmol/l, after 48 hours	n=17 10,4 (5;19,3)	n=13 24 (14,8; 32,6)	0,020
Change in urea concentration (T2-T1), mmol/l	-1,3 (-4,4; 1,99)	n=13 5,5 (-1,5; 12,2)	0,020
Creatinine, μmol/l, initially	n=17 108 (78; 150)	n=23 139,2 (75,5; 195)	0,373
Creatinine, μmol/l, after 48 hours	n=17 76 (64; 134)	n=13 148,3 (78; 255)	0,068
Change in creatinine concentration (T2-T1), μmol/l	n=17 -16 (-32; 5)	n=13 1,6 (-21; 81,3)	0,121
Serum iron, μmol/l, initially	n=8 5,5 (2,5; 8)	n=10 5 (2; 7)	0,525
Serum iron, μmol/l, after 48 hours	n=8 6 (3; 8)	n=9 5 (3; 6)	0,625
C-reactive protein, mg/l, initially	n=17 185 (32,6; 345)	n=20 200,25 (131; 401)	0,401
C-reactive protein, mg/l, after 48 hours	n=17 120,3 (12,7; 195)	n=14 129,5 (86; 200)	0,382
Change in the concentration of C-reactive protein (T2-T1), mg/l	n=17 -25 (-196; -4)	n=14 -29,6 (-105,3; 72)	0,404
Lactate, mmol/l, initially	n=14 3,6 (3,1; 4,5)	n=15 5,2 (4; 5,6)	0,004
Lactate, mmol/l, after 48 hours	n=14 2,75 (2,1; 3,6)	n=11 3,9 (3; 6,5)	0,011
Change in lactate concentration (T2-T1), mmol/l	n=14 -0,75 (-1,8; -0,1)	n=11 -0,9 (-1,9; 1,4)	0,602
Procalcitonin, ng/ml, initially	n=15 2,9 (0,5; 36,3)	n=19 3,25 (1,29; 12,1)	0,821
Procalcitonin, ng/ml, after 48 hours	n=14 3,795 (0,05; 8,38)	n=11 1,26 (0,5; 27,4)	0,761
Change in procalcitonin concentration (T2-T1), ng/ml	n=13 -1,7 (-16,3; -0,45)	n=11 -0,45 (-1,5; 12,53)	0,077

Note: T — research point: T1 — initial value and T2 — after 48 hours

Table 4. *Hematological parameters in patients with favorable and unfavorable outcomes*

Index	1. Patients with a favorable outcome Me (Q1; Q3)	2. Fatal patients Me (Q1; Q3)	p_{1-2}
IG%, initially	n=14 1,2 (0,7; 2,1)	n=19 0,8 (0,6; 1,5)	0,221
IG%, in 48 hours	n=14 1,5 (1; 3,2)	n=12 0,65 (0,45; 1,45)	0,023
IG#, 10^9/l, initially	n=14 0,08 (0,05; 0,19)	n=19 0,16 (0,07; 0,34)	0,465
IG#, 10^9/l, in 48 hours	n=14 0,165 (0,12; 0,25)	n=12 0,09 (0,035; 0,165)	0,041
Change IG# (T2-T1), 10^9/l	n=12 0,045 (-0,12; 0,19)	n=11 -0,03 (-0,16; 0,02)	0,165
Change IG# (T2-T1) в %	n=12 28,42(-44,44;348,33	n=11 -26,32 (-84,21; 22,22)	0,123
MCHC, g/l, initially	n=16 338 (331; 360,5)	n=20 334 (315,5; 345)	0,082
MCHC, g/l, in 48 hours	n=15 335 (332; 347)	n=13 328 (309; 333)	0,025
Change MCHC (T2-T1), г/л	n=13 -1 (-3; 4)	n=11 -5 (-13; 5)	0,416
% MCHC	n=13 -0,3 (-0,94; 1,2)	n=11 -1,43 (-3,45; 1,6	0,369
RDW-CV, %, initially	n=16 13,95(13,15;15,4)	n=20 15,95 (14,45; 17,55)	0,030
RDW-CV, %, in 48 hours	n=15 13,7 (13,3; 14,9)	n=13 15,9 (15; 17)	0,014
IRF, %, initially	n=9 10,9 (7,8; 15,6)	n=13 27,5 (16,1; 31,2)	0,005
IRF, %, in 48 hours	n=7 7,8 (4,8; 10,1)	n=10 20,8 (13; 28,7)	0,024
LFR, %, initially	n=9 87,8 (84,4; 90,5)	n=13 72,2 (68,8; 83,9)	0,004
LFR, %, in 48 hours	n=7 92,2(89,9;95,2)	n=10 83,6 (67,3; 90,9)	0,050
MFR, %, initially	n=9 9,6(8,1;13,9)	n=13 14,1 (13,1; 15,8)	0,021
MFR, %, in 48 hours	n=7 7,1 (2,5; 7,5)	n=10 11,45 (8; 17,8)	0,004
HFR, %, initially	n=9 1,6 (1,2; 1,7)	n=13 9,5 (2,8; 15,1)	0,029
HFR, %, in 48 hours	n=7 2,2 (0; 3)	n=10 7,7 (2,4; 11,9)	0,087
WBC, 10^9/l, initially	n=17 13,9 (7,33; 21,5)	n=23 17,09 (11,22; 22,33)	0,345
WBC, 10^9/l, in 48 hours	n=17 12,01 (7,77; 17,2)	n=14 14,13 (9,42; 17,5)	0,330
RET, %, initially	n=9 1,05 (0,78;1,41)	n=13 1,78 (1,09; 2,5)	0,052
RET, %, in 48 hours	n=7 0,68 (0,53; 0,82)	n=10 1,405 (0,56; 1,8)	0,063
RET, x10^9/l, initially	n=8 37,75 (26,5; 45,9)	n=13 75,5 (41,9; 83,2)	0,070
RET, x10^9/l, in 48 hours	n=7 22 (21; 46,3)	n=10 60,55 (49,1; 74,5)	0,039
Changing the number RET (T2-T1), x10^9/л,	n=7 -0,3 (-25,9; 2,2)	n=10 -11 (-17,8; 0,8)	0,922
Changing the number RET (T2-T1), %	n=7 -1,79 (-54,99; 5,77)	n=10 -13,37 (-26,61; 4,020)	0,845

Note: T — research point: T1 — initial value and T2 — after 48 hours; IG% — relative number of immature granulocytes in%; IG# — absolute number of immature granulocytes; MCHC — average hemoglobin content in erythrocyte; RDW-CV — erythrocyte distribution index; IRF — immature reticulocytes; LFR — low fluorescent (mature) reticulocytes; MFR — medium fluorescent reticulocytes (at the stage of intermediate maturity); HFR — highly fluorescent (very immature) reticulocytes; WBC — leukocytes; RET — reticulocytes.

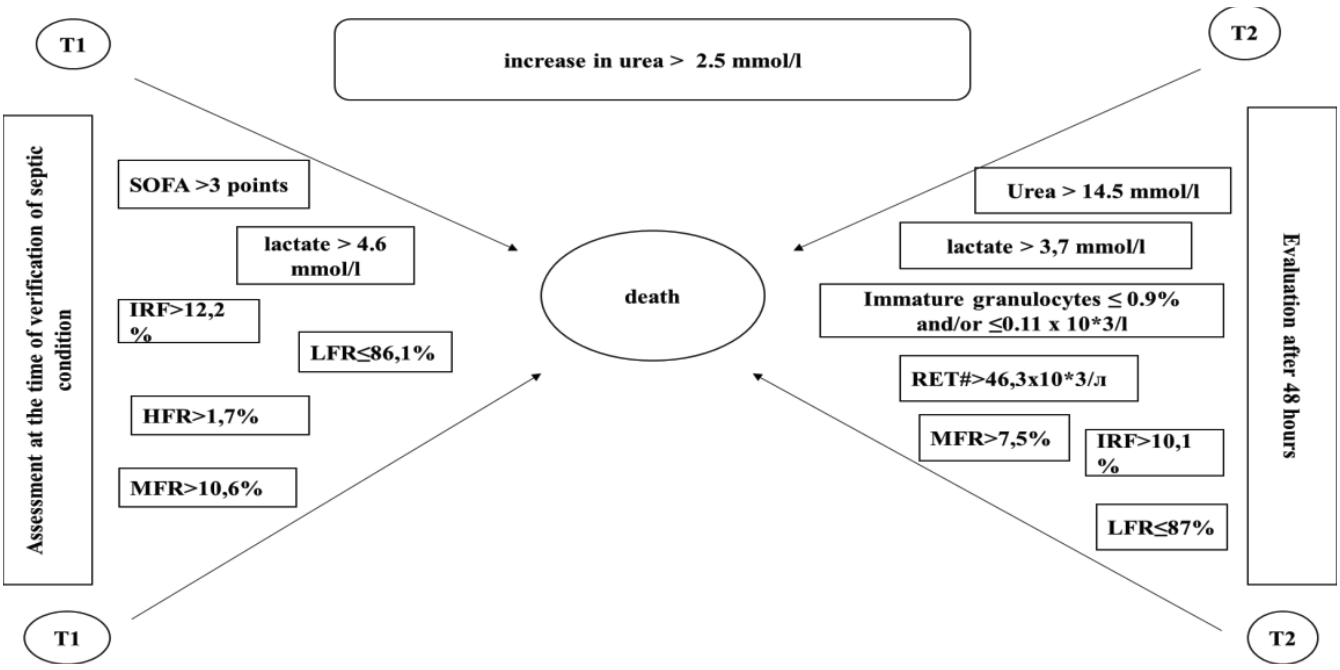

Figure 1. *Factors that increase the likelihood of death in respiratory sepsis*
Note: T1 — initial value and T2 — after 48 hours; SOFA — Sequential Organ Failure Assessment, organ failure rating scale, IRF — immature reticulocytes, LFR — low fluorescent reticulocytes, MFR — medium fluorescent reticulocytes, HFR — highly fluorescent reticulocytes, RET# — reticulocytes

- Relative count of low fluorescence reticulocytes (LFR, %): ≤ 86.1 % in point 1 (AUC 0.863 [95 % CI 0.650; 0.971], p = 0.0001, sensitivity 100 %, specificity 66.7 %) and ≤ 87 % in point 2 (AUC 0.786 [95 % CI 0.524; 0.943], p = 0.0171, sensitivity 70 %, specificity 85.7 %) is a predictor.
- Relative count of medium reticulocytes (MFR, %): > 10.6 % in point 1 (AUC 0.795 [95 % CI 0.571; 0.935], p = 0.0090, sensitivity 100 %, specificity 66.7 %) and > 7.5 % in point 2 (AUC 0.914 [95 % CI 0.676; 0.994], p = < 0.0001, sensitivity 90 %, specificity 85.7 %) is a predictor.
- Relative count of highly immature, high fluorescence reticulocytes (HFR, %): > 1.7 % in point 1 is a predictor (AUC 0.778 [95 % CI 0.552; 0.925], p = 0.0229, sensitivity 92.3 %, specificity 77.7 %.

For a schematic representation of identified critical values of factors, which increase the probability of death, please see Figure 1.

Discussion

Mortality levels in patients with pneumonia and sepsis are very high. A search for early predictors of death is very important. This study demonstrated that the total percentage of patients with pneumonia and sepsis who died was 57.5 %. According to WHO data for 2020, mortality among patients with sepsis, irrespective of the source of infection, was about 27 % in therapeutic wards in 42 % in ICUs [12].

According to a meta-analysis of 13 studies (80,520 subjects) to evaluate the role of gender as an independent prognostic factor of deaths in patients with sepsis admitted to ICUs, female patients had slightly higher all-cause mortality during a 28-day period (OR 1.18, 95 % CI 1.05–1.32) [13]. Despite the fact that in this study, the number of women in the group with poor outcome was slightly higher than men, no statistically significant differences were observed.

According to some authors, prognostic factors include SOFA score, dysfunction of more than two organs, origin of sepsis, lactate and urea levels [14-17]. The obtained results confirmed that the SOFA score of > 3 at diagnosis is a significant factor of poor outcome, with a high AUC value and high sensitivity. Serum lactate levels of > 4.6 mmol/L (baseline) and > 3.8 mmol/L (after 48 hours) have also proven to be predictive of poor outcome in patients with pneumonia-associated sepsis. This study demonstrated that urea concentrations of > 14.5 mmol/L in 48 hours after sepsis verification can be a prognostic marker of death. An increase in urea concentration of > 2.5 mmol/L

during 48 hours after the diagnosis was associated with mortality in the patients.

A brand-new predictor of poor outcome in sepsis can be immature granulocyte (IG) count. It has been proven that their higher count in infectious diseases and sepsis can be a marker of bacterial inflammation [18]. However, currently there are no published studies, where this parameter and its changes are seen as a major predictor of disease severity and poor outcome in patients with sepsis. In this study, immature granulocyte (IG) count of < 0.9 % of the leukocyte count and < $0.11x10^9$/L in peripheral blood 48 hours after sepsis verification was associated with death. The lack of an adequate increase in immature granulocyte levels in the general leukocyte population in patients with pneumonia at early stages of sepsis therapy can be indicative of depleted regenerating capabilities of the immune system as a result of limited proliferative functions of the bone marrow. Therefore, understanding how this biomarker behaves in sepsis can be an objective of future studies of disease outcome forecasting and assessment of drug therapy efficacy.

Also, the results of our study demonstrated the practicability of a dynamic assessment of erythropoiesis activity at early stages of pneumonia-associated sepsis, on the basis of a differential identification of reticulocyte maturity in peripheral blood. An increase in reticulocyte count in peripheral blood represents erythropoiesis activation in the red bone marrow, which is also typical for a number of severe infectious disease and their complications, including sepsis. For example, in a study by Tóth J. et al. (2017), sows with septic shock caused by Escherichia coli infection had a significant increase in blood reticulocytes 2 hours later [19]. A study by Buoro S. et al. (2017) of 62 ICU patients demonstrated that reduction in the relative reticulocyte count (%) was associated with a risk of a septic condition (OR = 0.35, 95 % CI 0.14–0.87) during the following 24 hours [20]. Currently, there is a limited number of published studies involving differential assessment of reticulocyte formation with identification of various reticulocyte maturity forms in sepsis. None of these studies assessed the role of such cells with various degrees of maturity as a potential predictor of deaths un patients with sepsis. In a study by Türkmen D. et al. (2021), a group of critically ill patients with sepsis had a higher immature reticulocyte fraction (IRF) vs healthy volunteers [21]. Therefore, our data are of special interest. A significant increase in immature reticulocyte fraction (IRF, %) in peripheral blood at early stages of sepsis and a reduced fraction of low fluorescence reticulocytes (LFR) can be associated with deaths in patients with sepsis and severe pneumonia. Additional studies are necessary to evaluate the practical significance of a differential assessment of reticulocyte maturity in sepsis. However, given a good availability of blood analysers, this approach can be justified in identification of patients at a high risk of death.

Conclusions

In order to identify groups at a high risk of death among hospitalised patients with pneumonia during the first 48 hours after sepsis diagnosis, such biomarkers as concentrations of urea, lactate, immature granulocytes and reticulocytes should be monitored over time, in addition to an assessment of organ dysfunction using SOFA scale.

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DOI: 10.20514/2226-6704-2024-14-2-144-153
УДК 616-006.441-085-06:616.12-07
EDN: YKJERL

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АССОЦИАЦИЯ КЛИНИКО-ДИАГНОСТИЧЕСКИХ ПОКАЗАТЕЛЕЙ КАРДИОВАСКУЛЯРНОЙ ТОКСИЧНОСТИ У ПАЦИЕНТОВ С НЕХОДЖКИНСКИМИ ЛИМФОМАМИ В ПРОЦЕССЕ ПРОГРАММНОЙ ПРОТИВООПУХОЛЕВОЙ ТЕРАПИИ

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Assessment of Clinical and Diagnostic Indicators of Cardiovascular Toxicity in Patients with Non-Hodgkin's Lymphomas in the Course of Programmatic Antitumor Therapy

Резюме

Цель исследования. Изучить ассоциацию клинико-диагностических показателей кардиоваскулярной токсичности у пациентов с неходжкинскими лимфомами, находящихся в процессе программной противоопухолевой иммунохимиотерапии. **Материалы и методы.** Проспективно было отобрано 72 пациента с подтвержденным диагнозом «индолентная неходжкинская лимфома», которым показано проведение противоопухолевого лечения по схеме R-CHOP. Пациенты были обследованы в два визита: V1 — на старте и V2 — после 6 курсов терапии. В процессе наблюдения пациенты были поделены на 2 группы: основную — с признаками сердечно-сосудистой токсичности (21 пациент, 16 (76,2 %) мужчин, средний возраст 55,2 (9,8) лет) и контрольную — без нее (51 пациент, 21 (41,2 %) мужчин, средний возраст 53,7(13,6) лет. Кардиоваскулярная токсичность верифицировалась на основании сочетания жалоб с изменениями в сократительной способности миокарда: снижения фракции выброса левого желудочка >10 % от исходного уровня или в абсолютном выражении менее, чем 53 % и/или снижения продольной систолической деформации левого желудочка >12 % от исходного уровня. **Результаты.** По окончанию основного лечения в обеих группах наблюдения отмечено статистически значимое увеличение QTc. Значимо менялось значение глобальной продольной систолической деформации левого желудочка у пациентов основной группы при одномоментном отсутствии ключевых сдвигов в отношении фракции выброса левого желудочка. Наиболее чувствительным лабораторным показателем кардиоваскулярной токсичности оказался NT-proBNP, концентрация которого статистически значимо увеличивалась у основной группы пациентов. **Заключение.** Расширение минимальной диагностической панели и комплексный подход к верификации кардиоваскулярной токсичности у пациентов онкогематологического профиля, получающих потенциально токсичную для сердечно-сосудистой системы терапию, позволит существенно улучшить показатели эффективности работы ключевых служб здравоохранения, снизить финансовые расходы на нивелирование осложнений и повысить качество жизни пациентов.

Ключевые слова: *кардиоваскулярная токсичность, кардиотоксичность, кардиоонкология, онкогематология, НХЛ*

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Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 09.02.2024 г.
Принята к публикации 25.03.2024 г.

Для цитирования: Гиматдинова Г.Р., Данилова О.Е., Давыдкин И.Л. и др. АССОЦИАЦИЯ КЛИНИКО-ДИАГНОСТИЧЕСКИХ ПОКАЗАТЕЛЕЙ КАРДИОВАСКУЛЯРНОЙ ТОКСИЧНОСТИ У ПАЦИЕНТОВ С НЕХОДЖКИНСКИМИ ЛИМФОМАМИ В ПРОЦЕССЕ ПРОГРАММНОЙ ПРОТИВООПУХОЛЕВОЙ ТЕРАПИИ. Архивъ внутренней медицины. 2024; 14(2): 144-153. DOI: 10.20514/2226-6704-2024-14-2-144-153. EDN: YKJERL

Abstract

Introduction. Standard antitumor immunochemotherapy used in the treatment of non-Hodgkin's lymphomas has clinically significant cardiovascular toxicity for patients. Modern medicine of the XXI century dictates the need for oncological specialists to closely monitor the state of the cardiovascular system of patients with malignant neoplasms, expanding the diagnostic panel with regard to early verification at the stage of subclinical changes. **The purpose of the study.** To study the association of clinical and diagnostic indicators of cardiovascular toxicity in patients with non-Hodgkin's lymphomas undergoing programmatic antitumor therapy. **Materials and methods.** 72 patients with a confirmed diagnosis of indolent non-Hodgkin's lymphoma were prospectively selected, who were shown to undergo antitumor treatment according to the R-CHOP scheme. The patients were examined in two visits: at the start and after 6 courses of therapy. During the follow-up, patients were divided into 2 groups: the main group with signs of cardiovascular toxicity (21 patients, 16 (76.2 %) men, average age 55.2 (9.8) years) and the control group without it (51 patients, 21 (41.2 %) men, average age 53.7 (13.6) years. Cardiovascular toxicity was verified based on a combination of complaints with changes in myocardial contractility: a decrease in the left ventricular ejection fraction >10 % from baseline or in absolute terms less than 53 % and/or a decrease in longitudinal systolic deformation of the left ventricle >12 % from baseline. **Results.** At the end of the main treatment, a statistically significant increase in QTc was noted in both follow-up groups. The value of global longitudinal systolic deformity of the left ventricle significantly changed in patients of the main group with the simultaneous absence of key shifts in relation to the ejection fraction of the left ventricle. The most sensitive laboratory indicator of cardiovascular toxicity was NT-proBNP, the concentration of which increased statistically significantly in the main group of patients. **Conclusion.** The expansion of the minimum diagnostic panel and an integrated approach to verifying cardiovascular toxicity in patients with oncohematological profile receiving potentially toxic therapy for the cardiovascular system will significantly improve the performance of key health services, reduce financial costs for leveling complications and improve the quality of life of patients.

Key words: *cardiovascular toxicity, cardiotoxicity, cardioncology, hematology, NHL*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 09.02.2024
Accepted for publication on 25.03.2024

For citation: Gimatdinova G.R., Danilova O.E., Davydkin I.L. et al. Assessment of Clinical and Diagnostic Indicators of Cardiovascular Toxicity in Patients with Non-Hodgkin's Lymphomas in the Course of Programmatic Antitumor Therapy. The Russian Archives of Internal Medicine. 2024; 14(2): 144-153. DOI: 10.20514/2226-6704-2024-14-2-144-153. EDN: YKJERL

CT — cardiovascular toxicity, ECG — electrocardiogram, TEE — transthoracic echocardiographic examination, NHL — non-Hodgkin lymphomas, stress-echoCG — echocardiographic stress test, LV EF — left ventricle ejection fraction, LV LD — longitudinal systolic deformity of left ventricle, NT-proBNP — N-terminal pro brain natriuretic peptide, type B, BMI — body mass index, ESD — end-systolic dimension, EDD — end-diastolic dimension, EDV — end-diastolic volume, ESV — end-systolic volume, LVMMI — left ventricle myocardium mass index, LA — left atrium volume, OT — outflow tract distal diameter, RA — right atrium volume

Introduction

In modern healthcare, full attention is given to the development of new drugs, which significantly improve overall survival of patients with malignancies. Despite better cancer therapies, some compounds used in the treatment of the target group have toxic effects on cell structures and the body in general. The most common adverse event associated with all antineoplastic drugs is cardiovascular toxicity (CT) [1]. Some chemotherapies have just limited cardiovascular effects, while others have broad effects and involve ion channels, receptors and neurotransmitters. Currently, various CT predictors have been studied: laboratory, instrumental, genetic. Patients undergoing anticancer therapy have a basic assessment of their cardiovascular function: electrocardiogram (ECG) recording, transthoracic echocardiographic examination (TTE), laboratory tests of some markers (highly-sensitive troponins, natriuretic peptides, etc.).[1]

In 2022, the number of newly diagnosed malignancies in the Russian Federation was 624,835, where 5.7 % accounted for lymphatic and blood-forming tissue conditions [2]. Among all hematologic malignancies, non-Hodgkin lymphomas (NHL) play a significant part; according to statistical records, NHLs were

[1] 2022 European Heart Journal, Volume 43, Issue 41, 1 November 2022, Pages 4229–4361, https://doi.org/10.1093/eurheartj/ehac244

verified in 544,000 patients worldwide [3]. Patients with confirmed NHL have several treatment options: standard chemotherapy, targeted radiation therapy, target drugs, haematopoietic stem cell transplantation or (a more common case) a combination of several options.[2] Obviously, due to some limitations (drug-related and/or professional), in regions of the Russian Federation, a commonly used option is standard antitumour immunochemotherapy, which combines several drugs, each of which affects the cardiovascular function ~~in its own way~~.

Study objective: To study the association between clinical and diagnostic parameters of cardiovascular toxicity in patients with non-Hodgkin lymphomas undergoing programmed antitumour immunochemotherapy.

Materials and Methods

Study design

A study was conducted over the period from January 2022 to September 2023, which assessed the association between clinical and diagnostic parameters of cardiovascular toxicity in patients with non-Hodgkin lymphomas undergoing programmed antitumour immunochemotherapy. The Federal State Budgetary Institution of Higher Education Samara State Medical University of the Ministry of Health of Russia and the State Budgetary Healthcare Institution Samara Regional Oncology Dispensary hosted an observational case-control study of 72 patients with confirmed non-Hodgkin B-cell lymphoma, cytologic type 1–2, who were prescribed 6 rounds of R-CHOP immunochemotherapy: Rituximab 375 mg/m^2 IV infusion (day 0 or 1), Doxorubicin 50 mg/m^2 IV infusion (day 1), Cyclophosphamide 750 mg/m^2 IV infusion (day 1), Vincristine 1.4 mg/m^2, no more than 2 mg in total (day 1), Prednisolone 100 mg per os (days 1–5); therapy was resumed on day 22. Inclusion criteria: patients over 18 years of age; confirmed target diagnosis and indications for therapy; no prior history of cardiovascular conditions; negative echocardiographic stress test (stress-echoCG); signed informed consent form. Non-inclusion criteria: patients less than 18 years of age; decompensated comorbidities; a history of cardiotoxic therapy; positive stress-echoCG. Exclusion criteria: complications which make it impossible to use scheduled therapy; emergence of conditions and/or diseases which are among non-inclusion criteria; patient refusal to undergo further assessments. The sample size was pre-calculated using MedCalc (version 20.104, MedCalc Software Ltd). With type I error of 0.05 and type II error of 0.2 (80 % power of the study) taking into account 30 % incidence of cardiac toxicity in the population and the ratio between both groups of 1 : 2, the sample size was 72 patients.

During the study, all patients were divided into two groups: study group included patients with CT manifestations (21 patients, mean age: 55.2 (9.8) (M (SD)) years old, including 16 males (76.2 %)), and controls, i.e. patients without cardiovascular complications (51 patients, mean age: 53.7 (13.6) years old, including 21 males (41.2 %)). According to Russian experts specialising in prevention, diagnosis and therapy of cardiovascular toxicity (2021), CT is verified if left ventricle ejection fraction (LV EF) is > 10 % of the baseline value, or, in absolute terms, less than 53 %, and/or reduction in longitudinal systolic deformity of left ventricle (LV LD) > 12 % of the baseline value [4]. Patients with these parametritic values of myocardial contractility combined with clinical signs were included in the study group. The study did not involve a detailed description of baseline clinical characterisation of patient groups (including analysis of arterial blood pressure) due to demonstration of a limited part of the work within the scope of clinical testing. The total duration of follow-up of each patient was 6 months. The primary end point was CT development.

Test methods

All patients had: complaint questionnaire; medical examination; 12-lead electrocardiogram (ECG) using Fukuda FX-7102 device (Japan, Fukuda Denshi Co.); TTE with LV LD assessment while lying on one side via left-sided parasternal and apical access using Mindray Resona I9 (China, Mindray)[3]; assessment of supposed laboratory markers of CT (troponin T, creatine phosphokinase, myoglobin, C-reactive protein, total cholesterol, N-terminal pro brain natriuretic peptide, type B (NT-proBNP)), in two stages: before therapy and after 6 rounds of therapy. Given the lack of patients from the moderate, high and extremely high CT risk groups at enrolment, changes in target parameters were assessed after completion of the main treatment. Obtained information was recorded in the case record form.

Ethics

This study presents a limited amount of information obtained during the clinical testing approved by the Ministry of Health of the Russian Federation in 2022, The Method of Early Diagnosis of Cardiac Toxicity in Patients with Indolent Non-Hodgkin Lymphoma. All enrolled patients signed voluntary informed consent in accordance with good clinical practice. Possible risks from participation in the study are similar to those in patients who were not included in the study. There are no additional risks from participation in the study.

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[2] 2020 Clinical Guidelines for Follicular Lymphoma https://cr.minzdrav.gov.ru/recomend/151_1

[3] Otto K. M. Textbook of Clinical Echocardiography, translated from English/ K. M. Otto; ed. M. M. Galaguza, T. M. Domnitskaya, M. M. Zelenikina, T. Yu. Kulagina, V. S. Nikiforova, V. A. Sandrikova. Moscow: Logosfera. 2019; 1352 p. ISBN 978-5-98657-064-8. EDN BUAHUQ.

Statistical analysis

Statistical processing of obtained results was performed using IBM Statistics SPSS, version 26 (USA). Data were assessed under parametric and non-parametric statistic methods. Quantitative variables were presented as arithmetic mean and standard deviation with normal distribution (M (SD), median (Me), 25th percentile and 75th percentile if an attribute was other than normal distribution; qualitative parameters — as an absolute number of patients and percentage (%). Among non-parametric statistic methods for two unrelated populations, Student t-test was used for normal distribution of an attribute, Mann–Whitney U test was used for non-normal distribution, while Wilcoxon rank sum test was used for related variables in two groups. The significance of differences in qualitative variables was assessed using cross tables. If the number of observations in any cell of these tables was at least 10, chi-square was used; for the number of observations from 5 to 9 — Yates' correction was applied; and where the number of observations was below 5 in any cell, then Fisher's ratio test was used.

The model was generated with the help of binary logistic regression. In order to evaluate the predictive value of the model, Nagelkerke coefficient of determination, sensitivity, specificity, prognostic value of a positive and negative result were calculated, and ROC analysis was performed with the calculation of AUC value. An analysis of the relationship between predictors included in the model and the probability of CT outcome is presented as odds ratio and their 95 % confidence interval; both unadjusted OR (determined using one-factor logistic regression) and adjusted OR (on the basis of a multifactor model) were calculated.

Differences were statistically significant at $p < 0.05$.

Results and Discussion

This was a study to analyse the association between clinical and diagnostic parameters of cardiovascular toxicity in patients with non-Hodgkin lymphomas undergoing R-CHOP antitumour therapy. All patients had their disease verified, met inclusion criteria, and did not present with any signs from the list of non-inclusion criteria. Table 1 contains results of a comparative analysis of the CT group and controls in terms of main clinical parameters.

Table 1. *Key characteristics of the patients included in the study*

Indicator	Main group, n=21	Control group, n=51	p — value
Age, full years*	55,2 (9,8)	53,7 (13,6)	0,597
BMI, kg/m^2	24,2 (22,1;27,4)	22,1 (20,9;24,4)	0,015
Gender, m/w, n (%)	16 (76,2) / 5 (23,8)	21 (41,2) / 30 (58,8)	0,007
Smoking, n (%)	10 (47,6) / 11 (52,4)	13 (25,5) / 38 (74,5)	0,095

Notes. * — quantitative features are presented in the form of an arithmetic mean and standard deviation M (SD)
Abbreviations: BMI — body mass index

Table 2. *The results of electrocardiographic examination in the study groups*

Indicator	Main group, n=21	Control group, n=51	p — value
HR before treatment, /min	75,0 (69,0;84,0)	70,0 (59,0;75,0)	0,033
HR after 6 courses of treatment, /min	74,0 (68,0;90,0)	75,0 (62,0;81,0)	0,413
	p=0,0709	p=0,043	
PQ before treatment, msec	120,0 (100,0;150,0)	147,0 (110,0;190,0)	0,087
PQ after 6 months of treatment, msec	110,0 (100,0;200,0)	160,0 (120,0;178,0)	0,232
	p=0,481	p=0,847	
QRS before treatment, msec	96,0 (90,0;100,0)	90,0 (80,5;100,0)	0,288
QRS after 6 months of treatment, msec	90,0 (80,0;100,0)	90,0 (80,0;100,0)	0,775
	p=0,460	p=0,809	
QTc before treatment, msec	360,0 (245,0;411,0)	333,0 (218,0;384,5)	0,193
QTc after 6 months of treatment, msec	411,0 (210,0;455,0)	345,0 (278,0;409,5)	0,139
	p=0,020	p=0,014	

Notes. * — quantitative features are presented in the form of an arithmetic mean and standard deviation M (SD)
Abbreviations: HR — heart rate; PQ — PQ interval; QRS — QRS complex; QTc — corrected QT interval

Table 3. *Echocardiographic parameters of the studied patients*

Indicator	Main group, n=21	Control group, n=51	p — value)
LVESD before treatment, mm	32,1 (32,0;39,0)	30,0 (27,0;32,8)	0,001
LVESD after 6 months of treatment, mm	34,0 (31,0;39,0)	30,0 (27,0;33,0)	<0,001
	p=0,686	p=0,886	
LVEDD before treatment, mm	49,0 (41,0;52,0)	45,0 (37,5;48,0)	0,03
LVEDD after 6 months of treatment, mm	46,0 (41,0;51,0)	44,0 (40,0;47,0)	0,135
	p=0,270	p=0,229	
LVMMI before treatment, g/m^2	89,0 (77,0;100,0)	74,0 (66,0;79,0)	<0,001
LVMMI after 6 months of treatment, g/m^2	87,0 (75,0;102,0)	72,0 (64,0;79,5)	0,002
	p=0,431	p=0,321	
LVEDV before treatment, ml	98,0 (90,0;114,0)	86,0 (71,0;97,0)	0,013
LVEDV after 6 months of treatment, ml	94,0 (77,0;110,0)	87,0 (73,5;94,5)	0,077
	p=0,244	p=0,118	
LVESV before treatment, ml	59,0 (47,0;71,0)	44,0 (31,5;49,0)	0,001
LVESV after 6 months of treatment, ml	52,0 (38,0;70,0)	41,0 (35,0;50,5)	0,019
	p=0,211	p=0,846	
LVEF before treatment, %	55,0 (52,0;63,0)	58,0 (53,0;63,0)	0,49
LVEF after 6 months of treatment, %	54,0 (45,0;61,0)	57,0 (52,0;61,0)	0,368
	p=0,217	p=0,079	
LA volume before treatment, ml/m^2	32,0 (31,0;35,0)	29,0 (27,0;32,0)	0,002
LA volume after 6 months of treatment, ml/m^2	32,0 (30,0;33,0)	27,0 (24,0;32,0)	0,015
	p=0,039	p=0,041	
VROT2 before treatment, mm	30,0 (29,0;33,0)	29,0 (27,0;32,0)	0,146
	31,0 (28,0;34,0)	29,0 (27,0;32,0)	0,136
VROT2 after 6 months of treatment, mm	p=0,835	p=0,732	
VROT1 before treatment, mm	25,0 (22,0;28,0)	22,0 (20,0;23,5)	0,002
VROT1 after 6 months of treatment, mm	24,0 (22,0;28,0)	22,0 (21,0;24,5)	0,037
	p=0,875	p=0,106	
RA volume before treatment, ml/m^2	29,0(25,0;32,0)	24,0(21,0;27,0)	0,002
RA volume after 6 months of treatment, ml/m^2	28,0(24,0;32,0)	24,0(21,0;27,5)	0,016
	p=0,888	p=0,041	
PA before treatment, mmHg	25,0 (22,0;28,0)	22,0 (17,0;27,0)	0,166
PA after 6 months of treatment, mmHg	24,0 (21,0;31,0)	22,0 (15,5;25,5)	0,108
	p=0,590	p=0,152	
GLS LV before treatment, %	|21,1 (19,7;22,4)|	|21,0 (20,5;22,0)|	0,921
GLS LV after 6 months of treatment, %	|17,0 (14,0;21,0)|	|20,7 (19,0;21,5)|	0,001
	p=0,003	p=0,080	

Notes. * — quantitative features are presented in the form of an arithmetic mean and standard deviation M (SD)
Abbreviations: LVESD — left ventricular end- systolic diameter; LVEDD — left ventricular end- diastolic diameter; LVMMI — left ventricular mass index of the myocardium; LVEDV — left ventricular end- diastolic volume, LVESV — left ventricular end- systolic volume; LVEF — the ejection fraction of the left ventricle; LA — the left atrium; VROT1 — distal right ventricular outflow tract; VROT2 — proximal right ventricular outflow tract; RA — the right atrium; PA — pulmonary artery; GLS LV — global longitudinal strain, longitudinal systolic deformity of the left ventricle

Table 4. *Laboratory indicators of the cardiovascular system*

Indicator	Main group, n=21	Control group, n=51	p — value
Total cholesterol before treatment, mmol/l	4,7(4,14;5,2)	4,1(3,41;4,45)	0,003
Total cholesterol after 6 months of treatment, mmol/l	5,2(4,4;7,9)	4,13(3,35;5,0)	0,002
	p=0,0110	p=0,030	
CPK before treatment, Units/l	110,0(97,0;114,0)	84,0(69,0;107,0)	0,033
CPK after 6 months of treatment, Units/l	91,0(57,0;109,0)	75,0(59,5;92,5)	0,321
	p=0,022	p=0,008	
CPK (MB) before treatment, Units/l	22,0(21,0;25,0)	16,0(12,0;21,0)	<0,001
CPK (MB) after 6 months of treatment, Units/l	22.0(21,0;31,0)	16,5(12,5;21,0)	0,002
	p=0,375	p=0,605	
Myoglobin before treatment, mcg/l	47,0(37,0;51,0)	39,0(27,0;50,5)	0,152
Myoglobin after 6 months of treatment, mcg/l	50,0(34,0;67,0)	41,0(22,5;52,5)	0,107
	p=0,422	p=0,521	
Troponin before treatment, pg/ml	10,1(8,7;12,4)	10,9(7,07;14,9)	0,771
Troponin after 6 months of treatment, pg/ml	10,5(7,18;31,2)	11,1(8,85;52,5)	0,724
	p=0,131	p=0,503	
CRP before treatment, mg/l	2,2(0,5;4,3)	3,1(1,06;5,35)	0,111
CRP after 6 months of treatment, mg/l	2,5(1,1;5,2)	3,2(2,05;5,25)	0,581
	p=0,204	p=0,564	
NT-proBNP before treatment, mg/ml	77,0(67,0;109,0)	74,0(46,5;100,5)	0,301
NT-proBNP after 6 months of treatment, mg/ml	154,0(73,0;765,0)	55,0(39,0;88,0)	<0,001
	p=0,008	p=0,237	

Notes. * — quantitative features are presented in the form of an arithmetic mean and standard deviation M (SD). Abbreviations: CPK — creatine phosphokinase; CPK (MV) — a form of creatine kinase found in the heart muscle; CRP — C-reactive protein; NT-proBNP — N-terminal propeptide of the B-type natriuretic hormone.

An assessment of the key comparative attributes in the groups demonstrated that patients were comparable in terms of potentially cardiotoxic therapy, age and smoking status ($p > 0.05$). Patients from the study group, who developed cardiovascular complications during therapy, had a higher baseline body mass index ($p = 0.015$), and males prevailed ($p = 0.007$).

An analysis of two-stage electrocardiographic parameters (Table 2) showed a lower pre-therapy heart rate (HR) combined with its relative increase in the control group, with single-point normal values. More prominent changes were observed in corrected QT interval (QTc): it was higher in both groups after antitumour therapy completion ($p = 0.020$ and $p = 0.014$, respectively). No statistically significant shifts were observed during the analysis of other parameters.

Table 3 shows echocardiographic data obtained during TTE.

A pre-therapy comparative analysis demonstrated that patients with CT had higher ($p < 0.05$) end-systolic dimension (ESD), end-diastolic dimension (EDD), end-diastolic volume (EDV), end-systolic volume (ESV), left ventricle myocardium mass index (LVMMI), left atrium volume (LA), outflow tract (OT) distal diameter, right atrium volume (RA) vs. controls, and studied parameters are within the normal population range[4]. After antitumour therapy completion and 6 months of follow-up, significant hemodynamic parameters ($p < 0.05$) still were ESD, ESV, LVMMI, LA volume, OT distal diameter, RA volume. It is also worth mentioning that LV LD was statistically lower ($p = 0.003$ and $p = 0.080$, respectively) in both groups as a result of the therapy with cardiotoxic compounds.

Myocardial contractility parameters were supplemented with results of a direct correlation analysis with potential laboratory markers of CT (Table 4).

According to study results, at the start of antitumour therapy, patients from the study group had higher total cholesterol, creatine phosphokinase (CPK) and CPK (MB) as compared to controls; however, values were within the normal range. Similar changes in total

[4] https://scardio.ru/content/Guidelines/recommendations_structure_heart_2012.pdf

cholesterol and CPK (MB) persisted in the study group after 6 rounds of antitumour therapy. Also, after 6 rounds of antitumour therapy, statistically significant increase in NT-proBNP level (p = 0.008) was observed in the study group.

One method to assess CT manifestations in all participating patients was collection of complaints about cardiovascular disorders (Table 5).

Since the primary division of patients was based on presence/absence of signs of CT, key clinical manifestations which were statistically significant were recorded mostly in the study group (p < 0.05). No statistically significant differences in thrombotic events were recorded between the groups.

We have developed a prognostic model for CT arising during 6 months after the therapy, depending on clinical and diagnostic factors, assessed before the therapy, under the binary logistic regression method. The resulting regression model is statistically significant (p < 0.001). Taking into account the Nagelkerke coefficient of determination, 70.7 % of CT dispersion is due to the factors included into the model. Characteristics of each factor are presented in Table 6.

The threshold value of logistic function P was 50 %. If P > 50 %, the risk of CT is high. If P < 50 %, the risk of CT is low. The sensitivity and specificity of the model with the mentioned threshold value were 66.7 % and 94.1 %, respectively. The positive and negative prognostic

Table 5. *Clinical manifestations of cardiovascular toxicity*

Indicator	Main group, n=21	Control group, n=51	P — value
Heart failure, n (%)	13 (61,9 %)	1 (2,0 %)	<0,001
Arterial hypertension, n (%)	17 (81,0 %)	2 (3,9 %)	<0,001
Edema, n (%)	8 (38,1 %)	1 (2,0 %)	<0,001
Thrombotic events, n (%)	3 (14,3 %)	1 (2,0 %)	0,072
Cardialgia, n (%)	11 (52,4 %)	1 (2,0 %)	<0,001
Hypotension, n (%)	4 (19,0 %)	0 (0,0 %)	0,006

Table 6. *Characteristics of the relationship of predictors with the probability of CT*

Predictors	Single-factor regression analysis		Multivariate regression analysis	
	COR; 95 % confidence interval	p-value	AOR; 95 % confidence interval	p-value
Gender	4,570; 1,450-14,40	0,01		
BMI, kg/m^2	1,140; 1,010-1,290	0,034	1,314; 1,074-1,609	0,007
Smoking	2,660; 0,920-7,690	0,072		
TC, mmol/l	2,770; 1,380-5,560	0,004	4,763; 1,427-15,90	0,011
KPC, Units/l	1,017; 1,001-1,034	0,041		
GLS LV, %	0,937; 0,727-1,208	0,616		
LVESV, ml	1,088; 1,039-1,140	0,001	1,126; 1,044-1,213	0,002
LVEDV, ml	1,028; 1,006-1,051	0,012		
LVESD, mm	1,203; 1,067-1,357	0,003	1,296; 1,081-1,553	0,005
LVESD, mm	1,087; 1,003-1,177	0,043		
LVMMI, g/m^2	1,084; 1,036-1,135	0,001		
NT-proBNP, mg/ml	1,003; 0,991-1,014	0,657		
Troponin, pg/ml	0,996; 0,899-1,037	0,34		
KPK(MB)	1,160; 1,040-1,280	0,005		
HR, /min	1,047; 1,009-1,088	0,016		

Notes. Abbreviations: BMI — body mass index; TC — total cholesterol; KPC — creatine phosphokinase; GLS LV — global longitudinal strain, longitudinal systolic deformity of the left ventricle; LVESV — left ventricular end- systolic volume; LVEDV — left ventricular end- diastolic volume, LVESD — left ventricular end- systolic diameter; LVEDD — left ventricular end- diastolic diameter; LVMMI — left ventricular mass index of the myocardium; NT-proBNP — N-terminal propeptide of natriuretic hormone B-type; heart rate — heart rate

values were 82.4 % and 87.3 %, respectively. The diagnostic value was 86.1 %.

The area under ROC curve, which corresponded to the relationship between CT prognosis and the value of the logistic regression function, was 0.948 (0.024) with 95 % CI of 0.900–0.995. The resulting model was statistically significant ($p < 0.001$).

Usually, the standard programmed antitumour therapy used for patients with non-Hodgkin lymphomas has the highest negative effect for the cardiovascular system. In a 2022 systematic review by Maria Adriely Cunha Lima et al., who analysed 32,009 patients with malignancies, just 2,255 cases (8.3 %) did not have CT [5]. Bin Lu et al. (2022), who evaluated the efficacy of the therapy of oncohaematological tumours and the impact of (R)-CDOP therapy on cardiovascular system in patients with non-Hodgkin lymphomas, established that the incidence of CT was 7.45 % (confidence interval (CI) = 4.86–10.44 %) [6].

Since such adverse events cause the need to reduce a drug dose and very often result in loss of response to the therapy, detection of subclinical changes to justify a cardioprotective strategy is important than ever. Currently, there are numerous Russian and foreign articles dedicated to attempted search for prognostic value of laboratory, instrumental and genetic predictors of CT.

One of the most common and widely used methods to detect cardiovascular changes in oncohaematological patients is ECG recording. Starting from 1990s, it was found out that some chemotherapy agents had considerable impact on QTc and cause fatal rhythm disturbances, including sudden cardiac arrest. In a 2017 systematic review of ECG changes in patients with malignancies who underwent a target therapy, prolonged QTc of > 500 ms was recorded in 5.4 % of patients with CT [7]. In this study including 72 patients with NHL, significantly prolonged QTc was recorded with an increase in the cumulative antitumour dose (from 360.0 (245.0; 411.0) to 411.0 (210.0; 455.0), with $p = 0.020$ in the study group, and from 333.0 (218.0; 384.5) to 345.0 (278.0; 409.5), with $p = 0.014$ in controls).

In all currently published textbooks in oncology and cardiology, standard TTE with LV EF assessment is recommended as a first-line method in CT screening. According to a large-scale work by Ainsley Ryan Yan Bin Lee et. al. (2023), the number of cases of an absolute reduction in LV EF by 10 % of the baseline value, or LV EF reduction below 50 % in patients undergoing therapy, including antracyclic antibiotics, was 17 % (CI: 11–24; 71 %) [8]. In a study by A. T. Teplyakov et al. (2019) of 176 women with breast cancer who were treated with antracyclic antibiotics as a component of antitumour therapy, no significant changes in LV EF (TTE results) vs. baseline data were recorded [9]. Normal LV EF

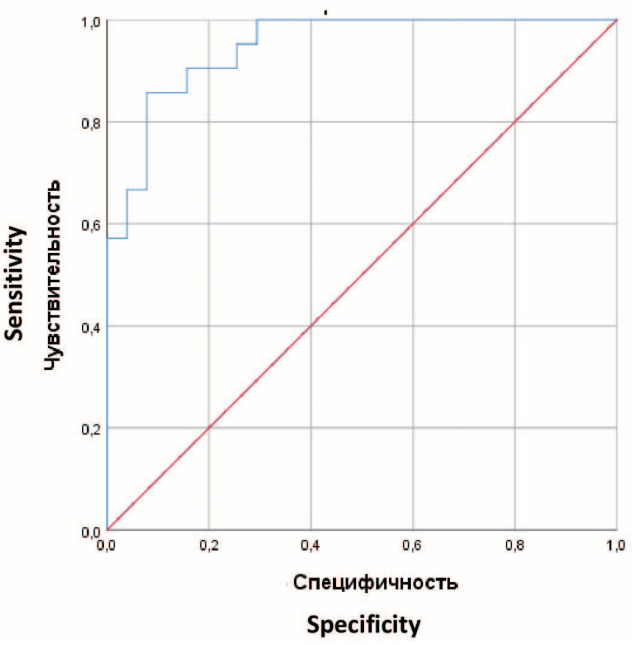

Figure 1. *Sensitivity and specificity of the model*

values were recorded in 40 breast cancer patients over a 6-month follow-up period in a paper by scientists from the Scientific Research Institute of Comprehensive Cardiovascular Issues [10]. In this study, patients with NHL treated with doxorubicin did not demonstrate statistically significant changes in LV EF over the entire follow-up period.

Given the variability of LV EF values in cancer patients, as well as parameter intactness before the myocardium is irreversibly damaged, modern medical literature recommends using more sensitive methods for CT diagnosis[5]. Currently, LV LD analysis is a very promising tool for verification of subclinical signs of cardiovascular toxicity. A study of myocardial contractility in 1,504 patients undergoing antitumour therapy demonstrated that reduction in LV LD value by 10–15 % during therapy is a more informative parameter in CT prognosis than a standard LV EF assessment [11]. This hypothesis is proven by a systematic review of 21 studies analysing 1,782 patients with malignancies, including breast cancer, haematological malignancies or sarcomas, who were treated with anthracyclines with or without trastuzumab [12]. Results of this study do not demonstrate any critical inconsistencies with global medical literature: patients with NHL demonstrated statistically significant reduction in LV LD values during antitumour immunochemotherapy (from |21.1 (19.7;22.4)| to |17.0 (14.0;21.0)|, with $p = 0.003$ in the study group, and from |21.0 (20.5;22.0)| to |20.7 (19.0;21.5)|, with $p = 0.080$ in controls).

[5] Eurasian clinical guidelines for cardiovascular complications of cancer treatments: diagnosis, prevention and treatment (2022)/ Chazova I. E., Ageev F. T., Aksenova A. V. [et al.] // European Heart Journal. — 2022. — No. 1(38). — P. 6-79. — DOI 10.38109/2225-1685-2022-1-6-79. — EDN SIVDQT.

As far as CT diagnosis on the basis of laboratory predictors is concerned, there is no consensus. A study by Russian scientists of patients treated with antracyclines, including 74 patients with non-Hodgkin lymphomas, demonstrated a significant increase in troponin I and NT-proBNP concentrations ($p < 0.0001$) [13]. According to foreign literature, NTproBNP values of > 900 pg/mL are a marker of severe cardiovascular events in patients with non-Hodgkin lymphomas [14]. At the same time, some studies confirm high sensitivity of NT-proBNP in CT; however, there are evidences of other causes of increased values of this parameter, including atrial fibrillation and valvular heart disease [15]. In this article analysing laboratory parameters in patients with NHL and verified CT, the most sensitive marker of cardiovascular dysfunction is NT-proBNP: a statistically significant increase of the value from 77.0(67.0;109.0) mg/mL to 154.0(73.0;765.0) mg/mL, with $p = 0.008$ in the study group (patients with CT), who had 6 rounds of antitumour immunochemotherapy, was recorded.

A limiting factor of this study is the lack of direct correlation analysis of a cardioprotective strategy and changes in laboratory and instrumental parameters; a relatively small sample size of patients (resulting from a limited cohort of patients without a history of cardiovascular disorders).

Conclusions

In this paper, a multifactor regression analysis of patients with indolent non-Hodgkin lymphomas demonstrated that some common risk factors of cardiovascular events before therapy with potentially cardiotoxic agents remain unchanged (sex, smoking status, total cholesterol, BMI). Also, larger values of ESV, LV ESD on TTE, which represent myocardial remodelling, at the start of antitumour therapy supplement information on the cardiovascular system functioning, allowing a healthcare professional to implement a timely cardioprotective strategy, even in low-risk patients. Currently, the matter of early verification of CT in oncohaematological patients appears relevant due to the need to improve the quality of life of patients, especially during relapse-free periods. The results for the target group show the need for extending the diagnosis protocol for cardiovascular complications by adding LV LD and NT-proBNP. Besides, a comprehensive approach to the assessment of cardiovascular system functioning will allow identifying subclinical changes, implementing a timely cardioprotective strategy in patients with malignancies, and reducing cancer-unrelated mortality.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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DOI: 10.20514/2226-6704-2024-14-2-154-160
УДК [[616.126-022.6-06:616.155.391]+616.37-006.6]-053.9
EDN: YMUOJS

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ИММУНОЛОГИЧЕСКИЕ МАРКЕРЫ У ПАЦИЕНТОВ С ГАСТРОЭНТЕРОЛОГИЧЕСКИМИ ПРОЯВЛЕНИЯМИ В РАЗЛИЧНЫЕ ПЕРИОДЫ COVID-19

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Immunological Markers in Patients with Gastroenterological Manifestations During Different Periods of COVID-19

Резюме

Цель исследования — оценить уровни иммунологических маркеров у пациентов, перенесших COVID-19 и имеющих гастроэнтерологические симптомы в различные сроки. **Материалы и методы**. На I этапе проведено ретроспективное исследование 785 медицинских карт пациентов, находившихся на стационарном лечении с 05.2020 по 12.2020 г. с диагнозом «Новая коронавирусная инфекция COVID-19» среднего и тяжелого течения. Основной задачей была оценка клинических симптомов с фокусом на выявление гастроэнтерологических проявлений COVID-19. После выписки из стационара через 3, 6 и 12 месяцев было проведено телефонное анкетирование с применением специально разработанного опросника сотрудниками кафедры внутренних болезней ФГБОУ ВО Башкирский государственный медицинский университет (БГМУ) МЗ РФ для выявления гастроэнтерологических симптомов, а также с использованием стандартного опросника оценки желудочно-кишечных симптомов GSRS (Gastrointestinal Symptom Rating Scale — Шкала оценки желудочно-кишечных симптомов) и Бристольской шкалы оценки кала. В опросе приняло участие 247 респондентов, после чего они были разделены на 3 группы по критерию наличия и длительности симптомов со стороны желудочно-кишечного тракта. 1 группа — пациенты, с сохраняющимися желудочно-кишечными симптомами в период от 4 до 12 недель (продолжающийся симптоматический COVID) — 30 человек; 2 группа — пациенты с длительностью желудочно-кишечных симптомов более 12 недель (постковидный синдром) — 75 человек. Контрольную группу (3 группа) составили 151 пациент, переболевший COVID-19 без развития постковидного синдрома. На II этапе в каждой группе пациентов были исследованы сывороточные концентрации иммунологических маркеров (интерлейкины (ИЛ) 4, 6, 8, 18; ревматоидный фактор, антитела к дезоксирибонуклеиновой кислоте (ДНК)). **Результаты.** Отмечается статистически значимое увеличение среднего возраста у пациентов 1 группы и 2 группы ($p=0,02*10^{-4}$ и $p=0,01*10^{-9}$), а также длительности госпитализации у 1-й группы пациентов в сравнении с группой контроля (p=0,04). Женщины преобладали как в 1-й (p=0,01), так и во 2-й группах (p=0,002). Сроки амбулаторного лечения до госпитализации составили в среднем 8,1 дней. В обеих группах пациентов отмечались статистически значимое повышение уровня ИЛ-18 ($p=0,095$; $p=0,88*10^{-9}$), в группе 2 выявлено повышение уровня ревматоидного фактора (p=0,044) в сравнении с группой контроля. Выявлено также статистически значимое повышение уровней ИЛ-6 в обеих исследуемых группах относительно группы контроля (p=0,020; p=0,000017), при этом средние значения находились в пределах референтных интервалов. **Выводы.** Таким образом, пациенты, перенесшие COVID-19 среднетяжёлого и тяжелого течения, подвержены развитию постковидного синдрома, в том числе, с гастроэнтерологическими проявлениями. Впервые выявлен повышенный уровень ИЛ-18 у данной категории пациентов, что может служить как диагностическим биомаркером, так и потенциальной мишенью таргетной терапии.

Ключевые слова: *COVID-19, постковидный синдром, желудочно-кишечный тракт, ИЛ-18*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 02.02.2024 г.
Принята к публикации 25.03.2024 г.

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Для цитирования: Садретдинова Л.Д., Ганцева Х.Х., Иткулов А.Ф. и др. ИММУНОЛОГИЧЕСКИЕ МАРКЕРЫ У ПАЦИЕНТОВ С ГАСТРОЭНТЕРОЛОГИЧЕСКИМИ ПРОЯВЛЕНИЯМИ В РАЗЛИЧНЫЕ ПЕРИОДЫ COVID-19. Архивъ внутренней медицины. 2024; 14(2): 154-160. DOI: 10.20514/2226-6704-2024-14-2-154-160. EDN: YMUOJS

Abstract

Materials and Methods. A retrospective study of 785 medical records of patients hospitalized between 05.2020 and 12.2020 with a diagnosis of moderate to severe new coronavirus COVID-19 infection was performed in phase I. The study was conducted. The primary objective was to evaluate clinical symptoms with a focus on detecting gastroenterologic manifestations of COVID-19. After discharge from the Covid hospital in 3, 6 and 12 months, a telephone questionnaire was conducted using a specially developed questionnaire by the staff of the Department of Internal Medicine of the FSBEU VO BSMU of the Ministry of Health of the Russian Federation to identify gastroenterological symptoms, as well as using the standard questionnaire for the assessment of gastrointestinal symptoms GSRS (Gastrointestinal Symptom Rating Scale) and the Bristol Stool Assessment Scale. 247 respondents took part in the survey, after which they were divided into 3 groups according to the criterion of presence and duration of gastrointestinal symptoms. Group 1 — patients with persisting gastrointestinal symptoms in the period from 4 to 12 weeks (ongoing symptomatic COVID) — 30 people; Group 2 — patients with duration of gastrointestinal symptoms more than 12 weeks (post-COVID syndrome) — 75 people. The control group (group 3) consisted of 151 patients who had survived COVID-19 without the development of postcoviral syndrome. At stage II, serum concentrations of immunologic markers (interleukins 4, 6, 8, 18; rheumatoid factor, antibodies to DNA,) were studied in each group of patients. **Results.** There was a statistically significant increase in the mean age in group 1 and group 2 patients (p=0.02*10-4 and p=0.01*10-9), as well as in the duration of hospitalization in group 1 patients compared to the control group (p=0.04). Women predominated in both groups 1 (p=0.01) and 2 (p=0.002). The time of outpatient treatment before hospitalization averaged 8.1 days. In both groups of patients there was a statistically significant increase in IL-18 level (p=0,095; p=0,88*10-9), in group 2 there was an increase in rheumatoid factor level (p=0,044) in comparison with the control group. A statistically significant increase in IL-6 levels was also revealed in both studied groups in comparison with the control group (p=0,020; p=0,000017), while the mean values were within the reference intervals. **Conclusions.** Thus, patients who have had moderate to severe COVID-19 are susceptible to the development of post-Covid syndrome, including gastroenterological manifestations. For the first time, an elevated level of IL-18 was detected in this category of patients, which can serve as both a diagnostic marker and a potential target for targeted therapy.

Key words: *COVID-19, long-covid, gastrointestinal tract, IL-18*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 02.02.2024
Accepted for publication on 25.03.2024

For citation: Sadretdinova L.D., Gantseva H.H., Itkulov A.F. et al. Immunological Markers in Patients with Gastroenterological Manifestations During Different Periods of COVID-19. The Russian Archives of Internal Medicine. 2024; 14(2): 154-160. DOI: 10.20514/2226-6704-2024-14-2-154-160. EDN: YMUOJS

WHO — World Health Organisation, IL — interleukin, TNF — tumour necrosis factor, ACE2 — angiotensin converting enzyme, CBC — complete blood count, BBA — biochemical blood assay, AST — aspartate aminotransferase, ALT — alanine aminotransferase, CRP — C-reactive protein, PCR — polymerase chain reaction, ECG — electrocardiography, CT — computer tomography, GSRS — Gastrointestinal Symptom Rating Scale LDH — lactic dehydrogenase, PCS — post-COVID syndrome, RF — rheumatoid factor

Introduction

The World Health Organisation (WHO) has officially announced the end of the coronavirus infection 2019 (COVID-19) pandemic; however, currently there are still a lot of open questions about the health condition of patients who had acute COVID-19. Up to a half of patients still have symptoms, which they had not had before the novel coronavirus infection, and symptoms can last for a long period of time after the infectious process resolution. According to the recommendations of the National Institute for Health and Care Excellence (NICE), ongoing (symptomatic) COVID is diagnosed in the presence of symptoms 4 to 12 weeks after disease onset; post-COVID syndrome (long COVID) is diagnosed if symptoms persist for over 12 weeks [1]. According to the definition by the WHO, the term "post-COVID syndrome" is used to define a totality of various long-lasting symptoms in some individuals after past COVID-19; usually, they are diagnosed by a healthcare professional at least 3 months after disease onset [2]. GIT clinical symptoms of COVID-19 include nausea, abdominal pain, loss of appetite, heartburn and constipations [3], and the majority of initial symptoms resolve in 3–6 months. However, according to a multicentre, retrospective study conduced in New York (2021), 20.5 % of subjects with long COVID had persistent diarrhoea, while 13.7 % of patients with long COVID experienced loss of appetite even 7 months after infection [4, 5]. A number of studies demonstrated that both mild and severe COVID-19 can result in a hyperinflammatory reaction, which manifests with higher levels of multiple cytokines, including interleukin-6 (IL-6), IL-8 and tumour necrosis factor (TNF-α) [6, 7]. Nevertheless, the data on changes in the cytokine regulation system are fragmented and relate mainly to the acute stage of disease. Developing knowledge in this area will ensure better understanding of the pathogenesis of post-COVID syndrome in order to develop prevention and therapy methods.

Objective: To assess levels of immunological markers in post-COVID-19 patients who had GIT symptoms at a various stage of the disease.

Materials and Methods

The COVID Hospital of the Clinics at the Bashkir State Medical University hosted a retrospective study of medical records of 785 patients who were undergoing inpatient treatment for moderate and severe novel coronavirus infection COVID-19 from May 2020 till December 2020. The mean age was 59 years old, including 571 (72.3 %) patients with moderate and 214 patients (27.2 %) with severe disease. In order to confirm COVID-19, all patients had an oropharynx+nasopharynx swab for SARS-CoV-2 by real-time polymerase chain reaction (PCR) (Intifica SARS-CoV-2 kit, Alkor Bio LLC, Russia). On the average, patients were hospitalised on day 7 after first symptoms. 341 subjects (43 %) were males. The most common comorbidities before COVID-19 infection were hypertensive disease (40 %), ischemic heart disease (17 %), and diabetes mellitus (types 1 and 2) (17 %). The main characteristics of subjects are presented in Table 1.

The study was conducted in two stages. At stage I, electronic medical records were analysed to assess clinical symptoms, mostly to identify GIT signs of COVID-19. During inpatient treatment, all patients had standard laboratory and instrumental tests, included in the Global Clinical Recommendations for Prevention, Diagnosis and Treatment of the Novel Coronavirus Infection, Version 1 (January 29, 2020). Laboratory tests included complete blood count (CBC); biochemical blood assay (BBA)(creatinine, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, electrolytes, albumin); C-reactive protein (CRP); polymerase chain reaction (PCR) tests for SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2, formerly 2019-nCoV) — enveloped virus single-strand (+) RNA virus. Instrumental examinations included lung computer tomography (CT), electrocardiography (ECG). Also, biological materials were sampled (an informed voluntary consent form was signed for research and biological material sampling); a biobank for biological material storage at -80° C was created; and a database was registered (Database Registration Certificate No. 2021620499 dated March 16, 2021). 3, 6 and 12 months after acute COVID-19 infection, a phone survey was conducted in accordance with a dedicated questionnaire developed by the staff of the Chair of Internal Diseases at the Bashkir State Medical University of the Ministry of Health of Russia, and also using a validated Russian version of the Gastrointestinal Symptom Rating Scale (GSRS) and the Bristol Stool Form Scale. The original questionnaire and the validated version of GSRS were used to find out common complaints and specific chronic or acute symptoms, which are typical for GIT involvement. The survey included 247 respondents, who were divided into study groups: group 1 — patients with GIT symptoms of COVID-19 persisting 4 to 12 weeks (current symptoms of COVID), 30 subjects; group 2 — patients with GIT symptoms lasting over 12 weeks (post-COVID syndrome), 75 subjects; group 3 — controls, no GIT symptoms, 151 subjects (stage I).

The main objective of stage II was to identify patients with genuinely GIT symptoms, since initially formed groups (stage I) had both current GIT symptoms and other symptoms (joint pain, shortness of breath, etc.); therefore, patients only with persistent GIT symptoms (gastroenterological monosyndrome) were selected for the study of immunological markers (measurement of interleukins (IL) 4, 6, 8, 18, rheumatoid factor (RF), anti-DNA antibodies). Immunological markers were measured by enzyme-linked immunosorbent assay (ELISA) using human blood sample using Vektor-Best reagent kit (Vektor-Best JSC, Novosibirsk, Russia) in order to determine IL-4 levels (sensitivity: 0.4 pg/mL, measurement range: 0–100 pg/mL (reference values: 0.00–4.00)), IL-6 (sensitivity: 0.5 pg/mL, measurement range: 0–300 pg/mL (reference values: 0.00–10.00)), IL-8 (sensitivity: 2.0 pg/mL, measurement range: 0–250 pg/mL (reference values: 0.00–12.00); IL-18 (sensitivity: 2.0 pg/mL, measurement range: 0–1,000 pg/mL (reference values: 0.00–260.00); RF (reference values: 0.00–10.00); and anti-DNA antibodies (reference values: 0.00–20.00). Tests and assessments were conducted at the unit of clinical laboratory diagnostics of the Clinics at the Bashkir State Medical University.

As a result, 20 patients from group 1 and 38 patients from group 2 were included in stage II; 30 patients were controls. Inclusion criteria for stage II of the study were: male and female patients aged 18 to 80 years old; persisting GIT symptoms lasting 4 to 12 weeks and 12 and over weeks after acute COVID-19 infection without any other signs of post-COVID syndrome (shortness of breath, joint pain, fever, etc.). Non-inclusion criteria for stage II were: age of over 80 years old; patients with a history

Table 1. *Characteristics of the total sample*

Options	General sample N=785
Age, years, Me [IQR]	59 [49; 67]
Hospitalization, days, Me [IQR]	11 [9; 14]
Time from the onset of symptoms to hospitalization, days, Me [IQR]	7 [6; 10]
Men, N (%)	♂341(43)

Note: N — Total quantity; Me [IQR] (Me is the median, IQR is the first and third quartiles).

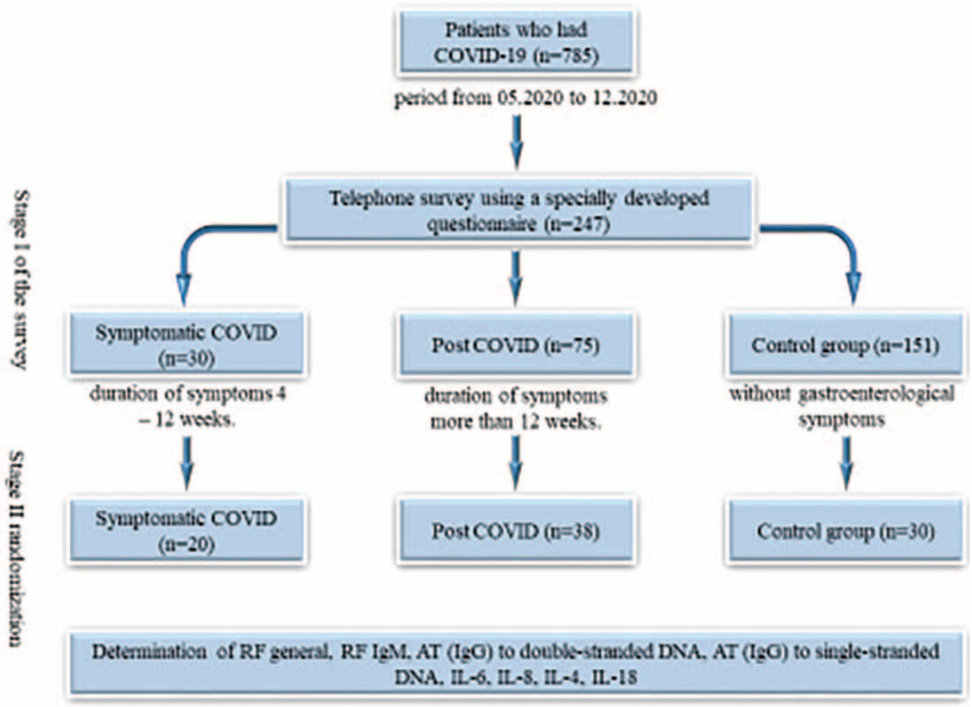

Figure 1. *Study design*
Note: Rheumatoid factor (RF), immunoglobulin G (IgG), antibodies (AT) IgG, interleukin (IL)

of GIT diseases before acute COVID-19; patients with other persistent symptomatic and post-COVID manifestations (shortness of breath, joint pain, fever, etc.); a history of/suspected malignancy in any location, any immunodeficiency; pregnancy, breastfeeding, a history of mental disorders; refusal from taking part in the study.

A schematic representation of the study is presented in Figure 1.

An informed consent form for the use of medical data for research purposes was signed both during inpatient treatment and, later, for the phone survey. The study was approved by the Local Ethics Committee at the Bashkir State Medical University (Minutes No. 4 dated April 21, 2021).

Statistical data processing was performed using Microsoft Excel 2010, Statistica 12.0. The normality of parameter distribution was assessed using Kolmogorov–Smirnov test. Depending on the normality of distribution, data are presented as median with quartiles and mean values with standard deviations. Intergroup pair-wise comparison of two independent samples was performed using Student t-test (for normal distribution) and Mann–Whitney U test (for distribution other than normal); statistically significant level was at $p < 0.05$. For qualitative data, 2x2 cross tables were used with Yates corrected $\chi 2$, if the frequency in at least one cell of the table was equal or less than 5. The degree of associations was assessed with the help of odds ratio (OR).

Results

Complaints of GIT problems, including abnormal bowel patterns and abdominal pain, were recorded in 11 % and 8 % of cases, respectively; the duration of symptoms was 4 [3; 4] and 2 [1; 2] weeks. The results are presented in Table 2.

Table 2. *Analysis of symptoms in patients who have had COVID-19*

Symptoms	N	%	Duration, weeks Me[IQR]
Weight loss (kg)	33	13	**7 [5; 10]**
Loss of smell	27	11	**4 [4; 12]**
Weight gain (kg)	27	11	**7 [5; 10]**
Abnormal stool (constipation/diarrhea)	27	11	**4 [3; 4]**
Loss of taste	22	9	**1 [1; 2]**
Stomach ache	21	8	**2 [1; 2]**

Table 3. *Results of a comparative analysis of clinical and anamnestic characteristics in the study groups at stage II*

Options	Group 1 N=20	Group 2 N=38	Control group N=30
Age, years	59,2±7,8* p=0,02x10^{-4}	56,2±6,5** p=0,01x10^{-9}	55,8 ±5,4
Hospitalization, days (Me±SD)	15,5±4,2* p=0,04	14±4,6	11,1±2,1
Time from the onset of symptoms to hospitalization, days Me [IQR]	**7 [5; 9]**	**7 [6; 10]**	**6 [5; 8]**
Men, N (%)	1(5)* p=0,01	6 (15,7)** p=0,04	12 (40)
Women, N (%)	19(95)	32 (84,3)	18 (60)

Note: N — Total quantity; p — statistical significance; Me+SD — mean + standard deviation; Me [IQR] (Me is the median, IQR is the first and third quartiles).
* Comparison of group 1 with the control group
** Comparison of group 2 with the control group

Table 4. *Analysis of the intensity of gastroenterological syndromes in the formed groups 12 months after acute COVID-19 infection*

Syndromes	Intensity, points Me [IQR]	
	Group 1 N=30	Group 2 N=75
Dyspeptic syndrome	**5 [5; 6]**	**5 [4; 6]**
Reflux syndrome	**5 [5; 7]**	**5 [4; 6]**
Abdominal pain syndrome	**6 [5,5; 6]**	**5 [4; 5]**
Constipation syndrome	**6 [6; 7]**	**6 [4; 7]**
Diarrheal syndrome	**5 [5; 6]**	**7 [5; 7]**

Note: N — Total quantity; Me [IQR] (Me is the median, IQR is the first and third quartiles).

Table 5. *Results of comparative analysis of immunological markers*

Options	Reference values	Group 1 N=20	Group 2 N=38	Control group N=30
RF total, U/ml M [Q1; Q3]	0,00-10,00	14,81; [13,63;20,59]* p=0,067	17,71; [13,39;21,21]** p=0,044	10,94; [7,64;18,3]
RF IgM, IU/ml	0,00-14,00	3,43; [1,45;13,01]	2,24; [1,32;4,36]	3,181; [1,78;4,11]
AT (IgG) to double-stranded DNA IU/ml	0,00-20,00	3,16; [1,89;9,54]	3,98; [1,54;7,24]	2,881; [1,45;5,12]
AT (IgG) to single-stranded DNA, IU/ml	0,00-20,00	2,88; [2,46;4,61]	3,86; [2,54;5,02]	3,885; [1,98;5,52]
IL-6, pg/ml	0,00-10,00	3,86; [2,27;4,29]* p=0,020	4,02; [3,32;4,2]** p=0,00017	0,96; [0,96;1,16]
IL-8, pg/ml	0,00-12,00	0,16; [0,01;1,37]	0,32; [0,01;1,78]	0,41; [0,01;1,78]
IL-4, pg/ml	0,00-4,00	0,48; [0,01;0,6]	0,48; [0,01;0,82]	0,20; [0,01;1,14]
IL-18, pg/ml	0,00-260,00	394,74*; [192,62;505,39] p=0,095	378,32*; [351,2;513,96] p=0,88x10^{-9}	121,16; [88;210,56]

Note: M[Q1; Q3] — median, first and third quartiles; N — Total Rheumatoid factor (RF), immunoglobulin G (IgG), antibodies (AT) IgG, interleukin (IL), deoxyribonucleic acid (DNA), international unit per milliliter (IU/ml), picogram per milliliter (pg/ml)
* Comparison of group 1 with the control group
** Comparison of group 2 with the control group

Statistically significant increase in the mean age of patients in group 1 and group 2 ($p = 0.02*10^{-4}$ and $p = 0.01*10^{-9}$), as well as duration of hospitalisation in group 1 vs controls ($p = 0.04$) were recorded. Females prevailed both in group 1 ($p = 0.01$) and group 2 ($p = 0.04$). Before hospital admission, outpatient treatment lasted on the average for 7 days. A comparative analysis of the study groups at stage II is presented in Table 3.

During the survey 12 months after acute COVID-19 infection, patients who had GIT symptoms, underwent an additional assessment of the nature and severity of complaints using the GSRS scale. The most common symptoms were heartburn (24 %), pain and discomfort in the upper section of abdomen (20 %), bloating (15 %), constipations (14 %), abdominal murmur (13 %), burping and bloating (9 %), hard stool (7 %); acid reflux (5 %), nausea and liquid stool (4 %). Also, the groups were assessed for the severity of GIT syndromes. The results are presented in Table 4.

Evaluation of the results of immunological biomarker assessment in group 1 and group 2 showed a statistically significant increase in serum IL-18 concentrations vs controls ($p = 0.095$ *and* $p = 0.88x10^{-9}$), respectively.

IL-18 levels were higher than the reference values in 8 patients (72 %) from group 1 ($p = 0.019$) and in 15 patients (88 %) from group 2 ($p = 0.014$).

It is important to note a higher serum IL-6 concentrations in the study groups ($p = 0.020$; $p = 0.000017$) vs controls, although they are within the reference range.

Total RF concentrations were statistically higher in group 2 patients ($p = 0.044$) vs controls. In group 1 patients vs controls, total RF levels demonstrated a trend ($p = 0.067$). The summary data on the comparative analysis of biological markers is presented in Table 5.

17 patients out of 20 in group 1 had higher rheumatoid factor values vs reference values ($p = 0.008$; OR = 7.41 (95 % CI 1.78–30.77), in group 2 patients — 32 patients out of 38 ($p = 0.001$; OR = 6.97 (95 % CI 2.24–21.63) vs controls.

Discussion

The study conducted in San-Paolo (Milan, Italy) in 377 patients has proven that over a half of individuals who had acute COVID-19 reported persistent symptoms for a certain period of time. Symptoms can last for 6–7 months and longer. In a multifactor analysis, female sex and elderly age were predictors of long COVID (OR = 3.3 and OR = 1.03, respectively), correlating with our results [8]. According to a systematic review and a meta-analysis by Choudhury A. et al. (2022), GIT symptoms of a past acute COVID-19 infection include abdominal pain (2.7 %), nausea and vomiting (4.6–10.3 %), diarrhoea (7.4–13.2 %) [9]. In this study, abdominal pain was recorded more frequently (8 %); the frequency of bowel disorders was comparable (11 %) with that of earlier studies. A majority of initial symptoms (abdominal pain, nausea, vomiting and diarrhoea) resolve in 3–6 months (in 90.5 % and 89.4 % of cases, respectively) [4]. In this study, complaints persisted for 5.17 ± 4.94 and 2.61 ± 2.34 weeks, respectively.

According to literature, patients with post-COVID symptoms had higher IL-6, SRP and TNF-α levels; and a higher IL-6 value was higher in all patients during 7 months after discharge from the hospital [10], correlating with our results. Also, we have found out higher rheumatoid factor values in patients with GIT symptoms of post-COVID syndrome. According to literature, higher levels of this biomarker were observed in patients with coronavirus infection both during the acute phase and for some time after the infectious process had resolved [11]. At the same time, the importance of RF assessment requires additional evaluation, since there is positive cross-reaction between rheumatoid factors and antibodies to Sars-Cov-2 virus [12].

According to Satış H. et al. (2021) [13], in patients with COVID-19, IL-18 levels correlated with IL-6 concentration, while baseline IL-18 values were a prognostic marker of severe disease. However, available literature does not contain any data on IL-18 levels in patients during various periods after COVID-19. In this study, evaluation of immunological biomarker assessment in group 1 and group 2 showed a statistically significant increase in serum IL-18 concentrations vs controls ($p = 0.095$ and $p = 0.88x10-9$), respectively. IL-18 levels were higher than the reference values in 8 patients (72 %) from group 1 ($p = 0.019$) and in 15 patients (88 %) from group 2 ($p = 0.014$).

Therefore, our results make it possible to better understand the immunopathogenesis of post-COVID syndrome; patients after the novel coronavirus infection had higher delayed IL-18 levels. Measurement of this biomarker is justified in this category of patients (invention patent No. 2807947. Method of Forecasting GIT Symptoms in Post-COVID Syndrome Using Immunological Markers) [14].

Conclusions

Therefore, patients who had moderate and severe COVID-19, are susceptible to post-COVID syndrome, including GIT manifestations. A higher IL-18 level in this category of patients has been identified for the first time; therefore, it can be used both as a diagnostic marker and a potential target in target therapy.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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