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УРОМОДУЛИН — БИОЛОГИЧЕСКАЯ ЗНАЧИМОСТЬ И ПЕРСПЕКТИВА КЛИНИЧЕСКОГО ПРИМЕНЕНИЯ

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Uromodulin — Biological Significance and Prospects for Clinical Use

Резюме

Уромодулин является уникальным белком, вырабатываемым в почках клетками эпителия восходящей толстой части петли Генле. Он реализует физиологические механизмы не только на канальцевом уровне, но и участвует в координации общеорганизменных процессов. Основными функциями уромодулина являются: препятствие камнеобразованию за счет нарушения агрегации солей кальция и реабсорбции воды, координация электролитного баланса, препятствие воспалительным процессам локально и системно. Экспрессия уромодулина и его качественные характеристики находятся под генетическим контролем. В связи с этим патология канальцевого аппарата или мутации генов, кодирующих уромодулин, приводят к развитию первичных или вторичных тубулопатий с дисфункцией других органов и систем. Вместе с тем известно, что уромодулин является не полностью изученным белком как по структуре, так и по особенностям выполняемых им функций. Проведен анализ научно-исследовательских сведений, в том числе экспериментальных работ по изучению уромодулина в отечественных и международных источниках литературы, с изложением полученного материла в данной рукописи.

Ключевые слова: *уромодулин, белок Тамма-Хорсфалла, структура, функции, тубулопатии, артериальная гипертензия, обмен ионов, камнеобразование, генетические мутации*

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Abstract

Uromodulin is a unique protein produced in the kidneys by epithelial cells of the ascending thick portion of the loop of Henle. It implements physiological mechanisms not only at the tubular level, but also participates in the coordination of general body processes. The main functions of uromodulin are an obstacle to prevent stone formation due to a violation of the aggregation of calcium salts and water reabsorption, coordination of electrolyte balance, and an obstacle to inflammatory processes locally and systemically. Moreover, the expression of uromodulin and its qualitative characteristics are under genetic control. In this regard, the pathology of the tubular apparatus or mutations in the genes encoding uromodulin lead to the development of primary or secondary tubulopathies with dysfunction of other organs and systems. At the same time, it is known that uromodulin is an incompletely studied protein both in terms of structure and features of the functions it performs. A thorough analysis of research data, including experimental work on the study of uromodulin in domestic and international literature sources, was carried out, with a presentation of the material in this manuscript.

Key words: *uromodulin, Tamm-Horsfall protein, structure, functions, tubulopathies, arterial hypertension, ion exchange, stone formation, genetic mutations*

Conflict of interests

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ADTKD — autosomal dominant tubulointerstitial kidney diseases, AKI — acute kidney injury, CKD — chronic kidney disease COX-2 — cyclooxygenase-2, ESRD — end-stage renal disease, GCKD — glomerulocystic kidney disease, GPI — glycosylphosphatidylinositol, HNF1β — hepatocyte nuclear factor 1β, IL-17, IL-23 — interleukin 17, interleukin 23, NKCC2 — Na + -K + -2Cl- cotransporter, ROMK — renal outer medullary K^+ channel, TAL — thick ascending limb of the loop of Henle, TLR-4 — toll-like receptor 4, TNF-α — tumor necrosis factor α, TRPM2 — transient receptor potential cation channel subfamily M 2, TRPV5/TRPV6 — transient receptor potential cation channel subfamily V member 5/6, UMOD — uromodulin gene, UTI — urinary tract infection, ZP — zona pellucida

Introduction

The history of uromodulin discovery goes back to 1873 when an Italian researcher Carlo Ravina isolated the protein cylindrin in urine and suggested that it was produced by urinary casts [1]. In 1950, Igor Tamm and Frank Horsfall established that human and animal urine contains a glycoprotein that could prevent viral hemagglutination [2, 3]. In 1985, A. V. Muchmore and J. M. Decker analyzing the urine of pregnant women revealed a protein that could suppress the expression of T-cells and monocytes [4]. Due to its local expression in renal tubules and the ability to regulate local immune response, the researchers named it uromodulin. In 1987, D. Pennica et al. discovered that uromodulin and the Tamm — Horsfall protein have the same amino acid sequence and, consequently, represent identical protein structures [2]. Later, Muchmore and Decker established that uromodulin had a high affinity with interleukin-1 and could be a soluble form of interleukin-1 receptors [5]. The interest in the properties of uromodulin and the specific features of its metabolism was the reason for its further detailed study as a potential marker of tubular dysfunction. The prognostic value of uromodulin is now considered not only in primary kidney diseases, but also in the early diagnosis of secondary nephropathies.

Specific Aspects of the Structure and Function of Uromodulin

Urinary protein spectrum is represented mainly by uromodulin. It is expressed only in kidneys, by epithelial cells of the thick ascending limb of the loop of Henle (TAL), and is secreted at an average rate of 50–100 mg/day [6, 7]. This explains the high prognostic value of uromodulin in the early diagnosis of tubular dysfunction of any etiology. A small part of uromodulin is also expressed in other tubular loci, however, this information is not generally acknowledged [8].

It should be mentioned that uromodulin is secreted in TAL in the endoplasmic reticulum as a precursor (84 kDa) that is subject to N-glycosylation, attachment to the apical surface of epithelial cells through its C-terminal propeptide, and connection with glycosylphosphatidylinositol (GPI). It should be emphasized that most part of uromodulin is expressed apically into the tubule lumen, and its small part has a basolateral secretion, i.e., in the interstitium. Then, when exposed to hepcidin, through a series of transformations, uromodulin is released from the GPI-precursor-uromodulin complex into the lumen of tubules in the form of homopolymer filaments about 2.5 μm long [9]. Uromodulin is defined in urine as a high molecular weight protein assembled

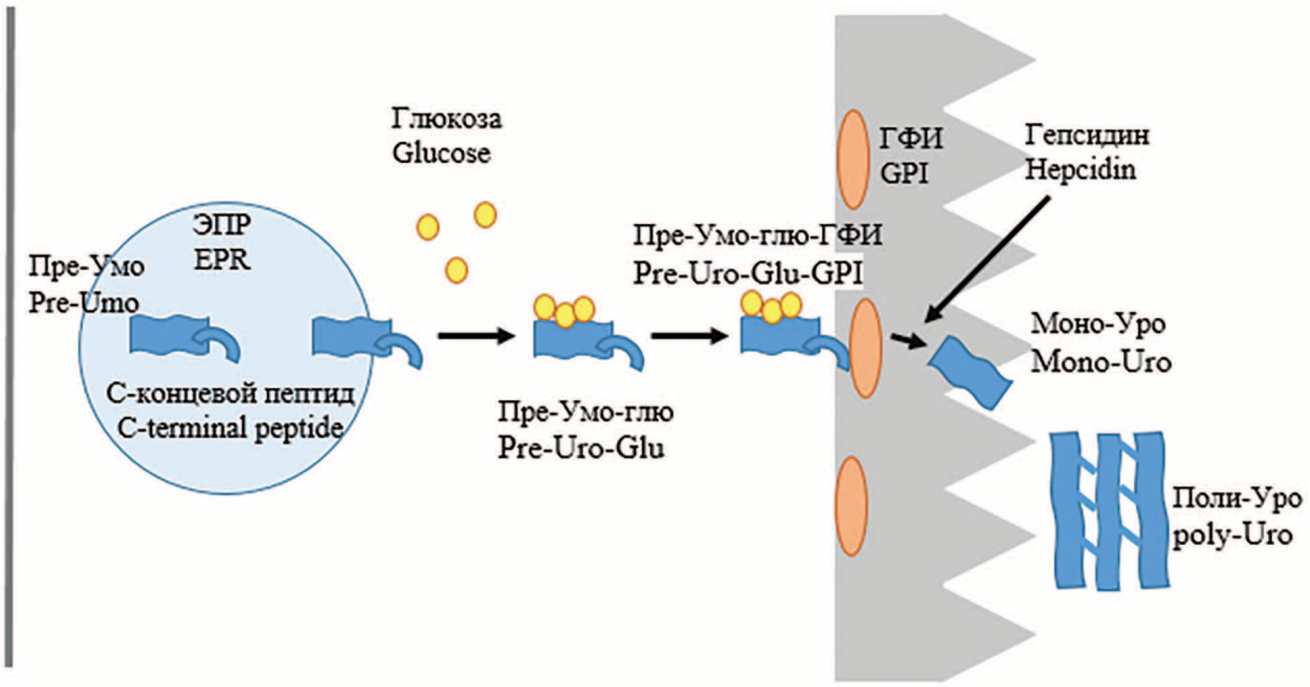

Figure 1. *Mechanism of uromodulin formation*
Note: EPR — endoplasmic reticulum, Pre-Umo — uromodulin precursor, Pre-Uro-Glu — glycosylated uromodulin precursor, GPI — glycoside phosphatidylinositol, mono-Uro — uromodulin monomer, poly-Uro — uromodulin polymer

into a polymer (Figure 1). Uromodulin development in the endoplasmic reticulum takes a long time; it is probably due to the complexity of the formation of tertiary structure [6].

Uromodulin includes three domains that are similar in structure to the epidermal growth factor and function as protein-protein interaction: central domain of 8 cysteines with still unclear function; zona pellucida (ZP) domain; complex for attachment to GPI [6]. The function of ZP domain is to perform protein polymerization processes, i.e., the formation of long filaments from homopolymers in urine. Uromodulin structure is characterized by a large amount of cysteine that, presumably, forms a complex three-dimensional protein structure due to disulfide bridges. Total amount of cysteine is 48 units with 616 amino acid bases [10].

Under normal conditions, hepcidin functions in tubular cell membrane. Hepcidin transforms the hydrophobic uromodulin molecule into a hydrophilic one by cleaving uromodulin and releasing ZP [11]. Thus, the outer hydrophobic area is blocked and the inner hydrophilic one is exposed [12]. Structural damage to tubular epithelial cells allows the development of functionally defective uromodulin molecule; it remains attached to the cell surface resulting in emerging low concentrations of uromodulin in urine.

The gel-like structure of uromodulin partially determines its important functionality, in particular, impaired aggregation of calcium salts and water reabsorption, management of electrolyte balance, and the relationship with pathogenic microflora.

Correlation between uromodulin and stone formation. The correlation between uromodulin secretion and stone formation is still the subject of scientific discussions. However, the large number of studies include data on a negative correlation between this protein and the risk of kidney stones. It has been established that uromodulin prevents the aggregation of calcium salts and promotes its absorption. However, most of the studies have been conducted in vivo in laboratory animals, and only several of them were performed in patients or in ionic solution in vitro, so, this is of research interest.

In the study by G. Pourmand et al. (2006), two groups of patients were compared that were ranked based on the presence of at least two episodes of oxalate stone formation and no history of nephrolithiasis [13]. There was no statistically significant difference in the average daily level of uromodulin in urine between two groups ($p = 0.53$). Meanwhile, a correlation was established between low levels of uromodulin and

the presence of bacteriuria in the group of patients with nephrolithiasis (p = 0.0001). The authors concluded that uromodulin can lead to aggregation of calcium salts in the presence of inflammation.

On the contrary, P. Tosukhowong et al. in their recent study (2018) confirmed elevated uromodulin levels in urine in patients with a history of oxalate stones who were previously prescribed limestone powder that neutralized oxalate precipitation [14]. In a review article by K. P. Aggarwal et al. (2013) on the effects of uromodulin, it is concluded that uromodulin inhibits the binding of calcium salts in human urine by attachment to the surface of calcium crystals, thus disrupting their aggregation [15]. In another in vivo experimental study on laboratory animals with knockout of the gene encoding uromodulin secretion, high calcium level in urine was determined that was associated with a high risk of stone formation compared with the control group; along with this, calcium precipitates were found in interstitium, renal medulla, tubules, and bladder [16–18].

The mechanism of stone formation, mainly of calcium oxalates, urates and phosphates associated with decreased secretion of uromodulin by tubular epithelial cells, has not been studied yet. Several factors were identified that associate the Tamm — Horsfall protein with nephrolithiasis.

First, uromodulin controls calcium reabsorption through epithelial channel TRPV5 (transient receptor potential cation channel subfamily V member 5), that is, it develops their receptor interaction. TRPV5 is a calcium-selective channel that allows transcellular transport from the apical to the basolateral surface of epithelial cell using a receptor mechanism. Evidence was obtained that the TRPV6 (transient receptor potential cation channel subfamily V member 5) channel that is a homologue of the TRPV5 channel and is heterogeneously associated with it, is also under the mediated control of uromodulin. Since calcium and sodium reabsorption are closely related, hypercalciuria and hypernatriuria are often found at the same time. This mechanism of electrolyte reabsorption is associated with a single Na-Ca exchanger that facilitates electrolyte transport through the cell. However, calcium transport in distal tubules is not associated with sodium reabsorption [19]. In this regard, uromodulin seems to play a key role in calcium transport through the cell. In a number of studies, it was found that hypercalciuria was detected in rats with a mutant type of uromodulin in the presence of normal sodium excretion in urine [20, 21].

Secondly, the uromodulin molecule in urine has a negative charge; it is directly related to the inhibition of calcium ion aggregation [1].

Thirdly, there is evidence that the component composition of urine affects kidney stone development, namely, qualitative and quantitative full value of present macromolecules. That is, the aggregation of calcium phosphate and oxalate takes place at a low concentration of uromodulin in urine, however, in the presence of other molecules that can inhibit or, on contrary, potentiate the aggregation process [22]. These molecules include, for example, osteopontin, bikunin, prothromin fragment 1, inter-alpha-trypsin [22]. This may explain the opposite results of the studies of the uromodulin effect on the possibility of stone formation.

The role of uromodulin in infectious, inflammatory and immune responses. The Tamm — Horsfall protein plays an important role in reducing the risk of urinary tract infections (UTIs) by its function as an antimicrobial protein. Uromodulin can capture bacteria using the polymeric structure of the protein, thereby inactivating the pathogenic properties of microorganisms. It is assumed that the high-mannose polypeptide chains of uromodulin are similar to the receptors on urothelium, and, using a competitive mechanism, they bind to the pili lectin of uropathogenic microflora (for example, *E. coli*), thereby impairing adhesion and colonization of urinary tract [10]. The studies conducted demonstrate a low probability of UTI development with underlying high level of uromodulin in urine regardless of the presence of conventional risk factors [23]. In laboratory animals with a defect in the gene encoding uromodulin expression, high titers of bacteria excreted in urine and severe pyelonephritis were found [24].

Moreover, the regulation of local immunity by uromodulin contributes to reducing the risk of developing infectious and inflammatory response of genitourinary system. The results of several studies demonstrate the role of uromodulin in the development of not only local, but also of systemic immune response. It is assumed that uromodulin functions upon activation of the macrophage system by increasing macrophage transcript and stimulating chemotaxis and phagocytosis [25, 26]. Data on the correlation between uromodulin secretion and neutrophilic infiltration of cells, monocytes and dendritic cells are presented. Uromodulin promotes the maturation of the latter via TLR-4 (toll-like receptor 4) signaling pathway, and thus additionally potentiates the activity of innate and acquired immunity [26]. Decreased concentration of uromodulin in urine is associated with higher levels of immunocompetent factors such as IgG28 (Immunoglobulin G 28), C3a (complement component 3a), C1q (complement component 1q), factor H and TNF-α (tumor necrosis factor-α) [27]. The relationship with proximal tubular

cells of S3 segment contributes to the suppression of the synthesis of renal cytokines in the presence of high uromodulin level in urine. It is also assumed that there is a relationship with systemic oxidative stress through the inhibition of TRPM2 (transient receptor potential cation channel subfamily M2) channels controlled by uromodulin [28]. Thus, uromodulin produces its nephroprotective effect in the cases of glomerulonephritis and tubulointerstitial nephritis. It is important to emphasize that not only urinary, but also serum uromodulin appears to be a promising biomarker for the progression of tubulointerstitial injury [28].

The mechanism of immune response regulation with uromodulin is not fully understood. An indirect interaction with immunocompetent cells or with their receptor apparatus is assumed.

There are also data on the regulation of systemic immune response by uromodulin. In the experimental study by R. Micanovic et al. (2015), the authors demonstrated that systemic neutrophilia developed with uromodulin deficiency [26]. The authors attributed the obtained data to the increased cytokine effect (IL-23, IL-17) in the absence of the sufficient control of uromodulin level emphasizing the role of kidneys in the regulation of not only granulopoiesis, but also of neutrophil homeostasis. The anti-inflammatory effect of uromodulin is also known; it is associated with the suppression of the activity of renal cytokines and lymphokines — interleukin-1, TNF-α [29].

It has been confirmed that ischemic damage to the tubules shifts the uromodulin expression from the apical surface of cell to the basolateral one; it indicates protein secretion into interstitial tissue in order to reduce the severity of its damage [29]. In a study conducted in a cohort of patients with sepsis but with no severe acute kidney injury (AKI), the data were obtained indicating that patients were more stable at higher blood concentrations of uromodulin [25]. Moreover, in a subgroup of patients with acute distress syndrome, uromodulin was isolated in the bronchoalveolar lavage of damaged lungs. It is important to note that AKI development was associated with a systemic decrease in uromodulin level and, as a result, with decreased immune response in general. The authors conducted a similar study on experimental animals with deficiency and normal expression of uromodulin in different variants of sepsis development. Attempts were made to treat them with the monomeric form of uromodulin; positive results in the form of improving the survival of animals were achieved. The authors convincingly show and present pathogenetically substantiated facts on the protective role of the uromodulin molecule excreted by kidneys during generalized inflammation [25].

Thus, uromodulin is, in particular, a promising biomarker for AKI, as well as chronic nephropathy of any origin. Development of drug products analogous to uromodulin will most likely help to solve the discussed clinical problems.

The role of uromodulin in homeostatic regulation. An important function of uromodulin is to control homeostasis by controlling the reabsorption of electrolytes such as sodium, potassium, and magnesium.

About 25 % of the filtered NaCl is reabsorbed in the thick ascending limb of the loop of Henle. Na + -K + -2Cl- cotransporter (NKCC2) is required to reabsorb NaCl in TAL; it also helps to reabsorb most part of sodium that is also expressed in TAL [30]. Uromodulin controls the function of NKCC2 and thus has an effect on reabsorption mechanisms. In an experimental study on laboratory rats with knockout for the gene expressing uromodulin, a subapical atypical accumulation of NKCC2 protein and its normal distribution on the apical part of epithelial cells [31]. Moreover, diuresis volume after intraperitoneal administration of furosemide was lower in the population of mice without uromodulin compared with the control group of healthy animals. The role of uromodulin in the functional coordination and other aquaporin and electrolyte channels was established. Thus, on the basis of experimental data, it was found that uromodulin promotes the expression of COX-2 (cyclooxygenase 2), thereby improving the function of aquaporin-2 and sodium-hydrogen exchanger [32]. In 2014, one of the journals of the American Heart Association (AHA) presented the information on the autocrine effect of TNF-α on the NKCC2 cotransporter that suppressed its activity [30]. Therefore, uromodulin binding to TNF-α allows additional control of sodium reabsorption.

The ability of uromodulin to directly or indirectly regulate the electrolyte exchange of potassium, chlorine, magnesium, and calcium ions in nephron tubules was established [32].

Uromodulin participation in the regulation of sodium reabsorption explains its role in the development of hypertension. It is known that in experiments on the potentiation of uromodulin expression and secretion, natriuresis and a tendency to hypotension developed [33, 34], and its deficiency resulted in hypertension [35–37].

Uromodulin ability to have an effect on the balance of reabsorption/excretion and other electrolytes was determined. To regulate the function of NKCC2, ROMK (renal outer medullary K^+ channel) and TRPM6 channels for the purpose of transcellular transport of magnesium, potassium, and calcium from the apical surface of distal tubular cells to the basolateral one, uromodulin expression is required [38–40].

Specific Aspects of the Genetic Control of Uromodulin Expression

Currently, there are more than 200 registered mutations of the gene encoding uromodulin expression and secretion (*UMOD*); they are localized in the 3rd, 4th, 5th, and 8th exons [32, 41, 42]. *UMOD* is located on chromosome 16p12.3 [41]. Mutation in *UMOD* leads to the impaired amino acid sequence of cysteine that is accompanied by changes in the protein folding sequence. Thus, immature uromodulin is developed that accumulates intracellularly in endoplasmic reticulum and is unable to be transported to the apical membrane of cells. Considering that the uromodulin molecule includes 48 cysteine residues linked by 24 disulfide bridges, modifications of genetic mutations are quite variable.

The high interest in uromodulin is also due to the development of rare kidney diseases that are usually associated with heterozygous mutations in *UMOD*. Monozygotic mutations are much less common [42]. Since the clinical course and pathophysiological mechanisms of these diseases are similar, a group of autosomal dominant tubulointerstitial kidney diseases (ADTKD) was identified that includes familial juvenile hyperuricemic nephropathy, type 2 medullary cystic kidney disease, and glomerulocystic kidney disease (GCKD) [41]. These rare diseases are considered to be uromodulin-associated. ADTKD are characterized by: hyperuricemia (including symptomatic one), interstitial fibrosis, tubular atrophy, and low urinary uromodulin level [43]. However, a wide variability in the clinical signs of ADTKD is described, even of its familial forms. The mechanism of tubular damage in ADTKD is centered around the accumulation of defective uromodulin in endoplasmic reticulum, as well as cell damage with further development of tubular and interstitial fibrosis, as well as cysts. All these processes lead to the development of chronic kidney disease (CKD) with different rates of progression.

In addition to the development of rare ADTKD, changes in the controlling *UMOD* are known that contribute to its uneven binding with its promoter, not to the impaired amino acid sequence of the protein. In this case, there is increased uromodulin expression and the development of salt-sensitive hypertension due to the activation of sodium chloride cotransporter (NKCC2) [42]. Hypertension is often accompanied by hyperuricemia that can be explained by increased reabsorption of urates together with sodium.

Obviously, the polymorphism of UMOD mutations is quite large and poorly known. There are questions regarding the implementation of the effects performed by defective uromodulin on the development of concomitant pathological processes and, most importantly, why one type of genetic mutations leads to the accumulation of defective uromodulin in endoplasmic reticulum with its decreased level in urine, while another variant, on the contrary, results in its increased expression?

Regulation of Uromodulin Expression and Secretion

Factors that regulate the expression and secretion of uromodulin are not well understood. In addition to genetic control, there are data on several factors of endogenous and exogenous stimulation of protein synthesis.

Thus, hepatic nuclear factor (HNF1β) binds to uromodulin DNA target regions and potentiates its expression [29]. Factors that increase uromodulin level in urine include excessive intake of NaCl and high-protein diets [29]. There is evidence of increased urinary calcium associated with increased concentration of uromodulin [44]. Considering the discussed functions of uromodulin, it can be assumed that increased potassium and chlorine levels may also have a positive correlation with this protein.

In the experimental study on laboratory rats, it was found that uromodulin level in urine decreased along with a decrease in COX-2 concentration. Moreover, the authors mentioned that low levels of uromodulin could result not from a direct effect of COX-2 deficiency, but from an indirect effect associated with TAL damage [45]. At the same time, factors leading to a decrease in uromodulin expression include the following: use of angiotensin converting enzyme inhibitors, colchicine, antidiuretic hormone, urinary tract obstruction, hypothyroidism [10, 29].

Prognostic Significance of Uromodulin and Its Possible Use

Compared to the biomarkers of glomerular damage, tubular biomarkers are not widely used in clinical practice. In this regard, uromodulin is a promising indicator of impaired renal function or damage due to the exclusive location of its secretion in nephron tubules.

Uromodulin appears to be a promising biomarker of tubular damage of any origin and of the progression of glomerular diseases with the development of the glomerular-tubular continuum. Decreased uromodulin level in the group of patients with CKD demonstrates an increased risk of developing end-stage renal disease (ESRD) [46, 47]. Moreover, there is evidence that uromodulin can be used as a biomarker in Fabry disease and active lupus nephritis [10].

Due to the establishment of a direct association with the parameters of glomerular filtration rate (GFR), it is obvious that low uromodulin concentration in urine can

Table 1. *Practical and scientific possibilities of using uromodulin*

№	Characteristic	Pathological conditions
I.	**Congenital pathologies associated with a defect in the uromodulin gene (*UMOD*)**	
1.	Gene mutations caused by a violation of the amino acid sequence of cysteine	Familial juvenile hyperuricemic nephropathy
		Medullary cystic kidney disease type 2
		Glomerulo-cystic kidney disease
2.	Decoupling of *UMOD* with the promoter	Salt sensitive hypertension
II.	**Acquired pathologies associated with impaired expression and secretion of uromodulin**	
1.	Violation of electrolyte homeostasis with a decrease in the concentration of uromodulin	Hypoelectrolytemia (sodium, potassium, magnesium, chlorine, calcium)
2.	Processes associated with infectious, inflammatory and immune responses	Increased risk of UTI with a decrease in the concentration of uromodulin
		Progression of GN, TIN
		Progression of inflammatory reactions in systemic inflammatory diseases (sepsis, ARDS)
		Development and progression of AKI
III.	**Stone formation (oxalates, urates, phosphates) with a decrease in the concentration of uromodulin**	Nephrolithiasis
		МКБ/ Urolithiasis disease
IV.	**Tubular damage and progression of glomerular lesions, including primary glomerular pathologies, with a decrease in the concentration of uromodulin**	Progression of primary and secondary nephropathy to terminal renal failure
		Marker of tubular injury, risk of terminal renal failure in Fabry disease
		Marker of tubular damage, risk of terminal renal in active lupus nephritis

Note: UTI — urinary tract infections, GN — glomerulonephritis, TIN — tubulointerstitial nephritis, ARDS — acute respiratory distress syndrome, AKI — acute kidney injury

be considered as an unfavorable predictor of decreased kidney function, in particular, of filtration function in secondary nephropathies. In some research papers, increased rate of CKD progression and increased overall cardiovascular risk is mentioned along with a decrease in uromodulin concentration in patients with cardiovascular diseases [48, 49].

In connection with the functions of uromodulin, low level of this protein in urine can be a biomarker for rare genetic anomalies (familial juvenile hyperuricemic nephropathy, type 2 medullary cystic kidney disease, glomerulocystic kidney disease). In those cases of hyperuricemic nephropathy in patients with gout, decreased urinary uromodulin/creatinine ratio was associated with the progression of CKD [50].

Uromodulin is mostly found in the apical surface of tubular cells, and to a lesser extent, in the basolateral one [51]. Excessive uromodulin in the basolateral part of cells is found during the development and progression, first of all, of the inflammatory process, as well as of the oxidative stress. Accumulating in the basolateral surface, uromodulin enters the interstitium and also elevates in systemic circulation. At the same time, the level of Tamm — Horsfall protein increases due to metabolic disorders and can lead to the development of "aggregates" potentiating stone formation and urinary tract obstruction. In this regard, the determination of uromodulin concentration in urine and in blood in patients with AKI or ischemic nephropathy seems to be prognostically significant.

It is established that uromodulin is also found in tubules between week 8 and 16 of gestation, and from week 20 — in the gestational waters of a pregnant woman [10]. In this case, uromodulin may also have prognostic potential as a marker for timely diagnosis of the developmental disorders of fetal tubular apparatus.

The information presented is shown in a table with the basic characteristics of uromodulin in practical and scientific context highlighted. It should be mentioned that considering the ongoing research on pathological and physiological responses associated with uromodulin, the data in the table have potential for scientific and clinical use.

Conclusion

A wide range of uromodulin functions, its mechanism of action, as well as the specific aspects of genetic control determine the wide potential of using this protein in clinical practice as a universal biomarker of kidney injury of various etiology. Further study of uromodulin and its role in metabolism will discover new potential predictive capabilities of the Tamm — Horsfall protein.

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ФАКТОР ДИФФЕРЕНЦИРОВКИ РОСТА-15 (GDF-15) КАК БИОЛОГИЧЕСКИЙ МАРКЕР ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

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Growth Differentiation Factor-15 (GDF-15) is a Biological Marker in Heart Failure

Резюме

Сердечная недостаточность является важной медицинской, социальной и экономической проблемой во всем мире. В последние годы был изучен ряд диагностических и прогностических биологических маркеров крови при сердечно-сосудистых заболеваниях. Идентификация новых биологических маркеров, анализ их патофизиологических аспектов и изменения концентрации под действием различных вариантов лечения, позволяют понять многие патогенетические особенности развития и течения сердечной недостаточности. Последние десятилетия в клиническую практику внедрены натрийуретические пептиды, широко используемые в качестве надежных биомаркеров для диагностической и прогностической оценки. Фактор дифференцировки роста-15 — цитокин, принадлежащий к семейству трансформирующих факторов роста, активность которого значимо повышается стрессе и воспалении. У пациентов с хронической сердечной недостаточностью концентрация данного биомаркера связана с повышенным риском общей летальности и неблагоприятными сердечно-сосудистыми событиями; у пациентов с сердечной недостаточностью с сохранной фракцией выброса левого желудочка использование биомаркера показало прогностическую и диагностическую значимость. Данные Фрамингемского исследования сердца показали, что фактор дифференцировки роста-15 был единственным биомаркером в многофакторном анализе, который продемонстрировал статистически значимую связь со всеми неблагоприятными сердечно-сосудистыми событиями. В 8 исследованиях показано, что избыточная экспрессия фактора дифференцировки роста-15 была связана с повышенным риском смертности у пациентов с сердечной недостаточностью. ~~Показано, что~~ Фактор дифференцировки роста-15 как прогностический биомаркер у пациентов с острой сердечной недостаточностью не уступает предшественнику мозгового

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натрийуретического пептида. Для подтверждения ценности определения в крови данного биомаркера у пациентов с сердечной недостаточностью необходимо проведение обширных проспективных рандомизированных клинических исследований.

Ключевые слова: *хроническая сердечная недостаточность, фракция выброса левого желудочка, биомаркеры, фактор дифференцировки роста-15*

Конфликт интересов

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

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Abstract

Heart failure is an important medical, social and economic problem around the world. In recent years, a number of diagnostic and prognostic biological markers of blood in cardiovascular diseases have been studied. Identification of new biological markers, analysis of their pathophysiological aspects and changes in concentration under the influence of various treatment options, allow us to understand many pathogenetic features of the development and course of heart failure. In recent decades, natriuretic peptides have been introduced into clinical practice, which are widely used as reliable markers for diagnostic and prognostic assessment. Growth differentiation factor-15 is a cytokine belonging to the family of transforming growth factors, the activity of which is significantly increased under stress and inflammation. In patients with chronic heart failure, the concentration of this marker is associated with an increased risk of overall mortality and adverse cardiovascular events; in patients with heart failure with preserved left ventricular ejection fraction, the use of the marker showed prognostic and diagnostic significance. Data from the Framingham Heart Study showed that growth differentiation factor-15 was the only marker in multivariate analysis that showed a statistically significant association with all adverse cardiovascular events. Eight studies showed that overexpression of growth differentiation factor-15 was associated with an increased risk of mortality in patients with heart failure. It was shown that growth differentiation factor-15 as a prognostic marker in patients with acute heart failure is not inferior to the brain natriuretic peptide precursor. To confirm the value of this marker in blood in patients with heart failure, it is necessary to conduct extensive prospective randomized clinical trials.

Key words: *chronic heart failure, left ventricular ejection fraction, biological markers, growth differentiation factor-15*

Conflict of interests

The authors declare no conflict of interests

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CHF — chronic heart failure, CRP — C-reactive protein, DD — diastolic dysfunction, Gal-3 — galectin-3, GDF-15 — growth differentiation factor-15, HF — heart failure, IR, I/R — ischemia-reperfusion injury, LVEF — left ventricular ejection fraction, NT-proBNP — N-terminal pro-brain natriuretic peptide, ST2 — stimulating growth factor

Introduction

Heart failure (HF) is one of the world's pressurizing medical, social and economic problems [1]. The prevalence of HF in the adult population of developed countries is about 2–3 %. The risk of developing chronic heart failure (CHF) in patients over the age of 60 is more than 10 % [1]. According to EPOKHA-AG and EPOKHA-CHF studies, the prevalence of CHF in Russia approximates 7 % [2].

Identification of new biological markers, as well as the analysis of their pathophysiological role and changes in their levels under various treatment options allowed understanding many pathogenetic aspects of the development and course of HF [3]. Currently, the assessment of the level of brain natriuretic peptide (BNP) and its N-terminal precursor (NT-proBNP) is a kind of "gold standard" for diagnosing HF and predicting its course, however, limitations due to the impact of many factors, the ambiguity of threshold values, and sufficiently low information value in cases of CHF with preserved left ventricular ejection fraction (LVEF) contribute to the need for further search for highly sensitive and specific laboratory biomarkers [3, 4]. New biological markers such as fibrosis marker galectin-3 (Gal-3), peptide hormone

adrenomedullin, stimulating growth factor ST2, chemokine CX3CL1, vasopressin surrogate marker, and others are increasingly used in real clinical practice [3, 4]. A multibiomarker approach is also important for diagnosis of CHF, stratification of its risk, and evaluation of the effectiveness of the treatment prescribed [3, 4].

It is commonly known that inflammation is a common response of a living organism to various damaging factors and is aimed at restoring tissue integrity and minimizing cell death. An active role in inflammatory response is played by pro-inflammatory cytokines, particularly, interleukins (IL-1, IL-2, IL-6, IL-8), tumor necrosis factor-α (TNF-α), chemokines and their receptors, cell adhesion molecules, as well as the acute-phase proteins (C-reactive protein (CRP) and pentraxin 3 (PTX3)). Pro-inflammatory cytokines activate fibroblasts and cardiomyocytes in the area of inflammation. The activated cells then produce cytokines and growth factors that function as powerful chemotactic molecules that enhance inflammatory response. Neutrophils and monocytes secrete transforming growth factor-β (TGF beta), as well as growth differentiation factor15 (GDF-15) that inhibits macrophage response and the synthesis of proteolytic enzymes. Inflammatory reactions in CHF result in the damage to cardiomyocytes, their apoptosis, and activation of neurohumoral systems that trigger reactions of myocardial hibernation and its remodeling [5].

The objective of this review is to consider GDF-15 as a diagnostic and prognostic marker in HF.

Sourcing Methodology

This article presents the review of publications over the recent 10 years. The analysis of literature sources was carried out using PubMed, RSCI, MedLine, Google Scholar, Science Direct databases. The authors reviewed both foreign and Russian papers. The search was carried out using the following keywords: biomarkers, heart failure, growth factor of differentiation 15.

Structure and Functions of GDF-15

GDF-15 is a cytokine that belongs to the family of transforming growth factor beta (TGF-ß) [6]. Under physiological conditions, the concentration of this biomarker in blood plasma and most tissues of the body is minor. GDF-15 was discovered more than twenty years ago; it was previously called macrophage inhibitory cytokine-1 (MIC-1) due to its possible role of the antagonist of macrophage activation by inflammatory cytokines (interleukins and tumor necrosis factors). The detailed mechanism of functioning of this biomarker in human body has not been fully established. GDF-15 receptor, its signaling pathways and biological aspects are not actually understood. Cytokine expression is activated by stress or tissue damage and is associated with inflammatory conditions of different organs, including myocardium [7, 8].

In animal models, GDF-15 was originally described as a cardioprotective protein that prevents cell death. The elevated expression of this biomarker is observed in response to harmful stimuli such as pressure overload or tissue ischemia. Activation of the enzyme nitric oxide synthase (NOS-2) in stressful situations leads to the increased production of GDF-15 [6]. The results of experimental studies of genetically modified rats with GDF-15 deficiency established its protective role in myocardial damage [6]. Th elevated cytokine level in the cardiomyocytes of rats with decreased activity of growth hormone was also demonstrated; this fact indicates ~~its~~ the involvement of GDF-15 in signaling pathways activated by growth hormone [6].

The human GDF-15 locus was mapped by fluorescence in-situ hybridization (FISH) to chromosome 19p12.1-13.1; it was shown that the gene contained a single intron [6]. The human GDF-15 promoter has binding sites for several transcription factors, including the cell cycle regulatory transcription factor p53 protein, early growth response protein 1 (Egr1), cyclic adenosine monophosphate response element-binding protein (CREB), transcription factor Sp1, cyclic adenosine monophosphate-dependent transcription factor (ATF-3), C/EBP homologous protein (CHOP). GDF-15 expression is increased by peroxisome proliferator-activated receptor (PPAR) γ-ligands. Several polymorphisms in the GDF-15 gene were identified. GDF-15 is synthesized as a precursor protein (pro-GDF-15) with the weight of ≈40 kDa that subsequently undergoes disulfide dimerization. The unprocessed translated form of GDF-15 (pre-pro-GDF-15) has the length of 308 amino acid residues including a signal sequence (29 amino acids), a propeptide (167 amino acids), and a mature protein (112 amino acids) with a cystine knot that is typical for TGF-β. The mature protein is secreted as a homodimer bound by disulfide bonds and is released from the propeptide after intracellular cleavage [7].

Method for Determination of GDF-15 in Blood

The level of this biological marker is determined using the immunoradiometric assay to determine the amount of radioactively labeled antigen-antibody complex by enzymes or luminescence (chemiluminescence). The detection range is 400–20,000 ng/L; at good accuracy and reproducibility, the error is less than 10 % [8, 9].

GDF-15 and Heart Failure

The elevated cytokine concentration is associated with cancer, insulin resistance, type 2 diabetes mellitus, renal dysfunction, cardiac diseases, and overall mortality; moreover, the level of this biomarker increases with age [10–15]. Examination of children with congenital heart diseases and HF revealed significantly higher GDF-15 blood concentrations compared to healthy children [15].

In a number of studies, the levels of GDF-15 and BNP/NT-proBNP in different groups of patients with CHF were evaluated. The authors concluded that NT-proBNP levels were higher in HF patients with reduced LVEF (HFrEF) compared with patients with preserved LVEF (HFpEF); however, GDF-15 concentration was elevated in patients with both systolic and diastolic LV dysfunction. Moreover, GDF-15 was found to be an important biomarker of adverse cardiovascular events and mortality and independent on LV contractility and NT-proBNP concentration [17–21]. The evaluation of GDF-15 level at different CHF stages revealed that the cytokine is a biomarker indicating the progression of the disease; its concentration increases at an exponential rate with an increase in the functional class (FC) of CHF (according to New York Heart Association (NYHA) classification) and the severity of LV remodeling. An elevated level of the biomarker was observed at the preclinical stage of heart failure [22].

According to H. Du et al. (2020), the results of the examination of 300 patients with ischemic HF revealed the level of GDF-15 that amounted to (582.6 ± 104.4) pg/mL in patients with HF FC IV and (408.4 ± 94.8) pg/mL in patients with NYHA functional class I HF [23].

First major study on the predictive value of GDF-15 in CHFnEF was carried out on the basis of Valsartan Heart Failure Trial (Val-HeFT) protocol (a study of using valsartan in the patients with CHF). GDF-15 levels were assessed at baseline and after 12 months of follow-up; 85 % of patients had elevated levels of GDF-15 biomarker (> 1,200 ng/mL). The results of a multivariate statistical analysis that included clinical parameters, BNP, troponin, and CRP levels revealed that high concentrations of this biomarker were independently associated with the elevated risk of all-cause mortality (OR 1.007; 95 % CI: 1.001–1.014; p = 0.02), but not with subsequent adverse events (OR 1.003; 95 % CI: 0.997–1.008; p = 0.34) such as sudden death, acute HF, and the need for inotropic support. After 1 year of follow-up, a comparable increase in GDF-15 level was observed in the placebo group and in the group of patients treated with valsartan. The levels of this biological marker were independently associated with all-cause mortality and with first adverse cardiovascular event. There was no change in GDF-15 level due to HF treatment [15].

In the PARADIGM-HF study (sacubitril/valsartan compared with enalapril in patients with HFnEF), GDF-15 levels were determined in 1,935 patients. Its baseline values, as well as values after 1 month and 8 months of treatment were associated with the elevated risk of overall mortality, adverse cardiovascular events (CVS), and with cardiovascular mortality or hospitalization for decompensated CHF. There was no change in GDF-15 concentration associated with drug administration [24].

P. Foley et al. (2009) in their study evaluated GDF-15 level during cardiac resynchronization therapy. 72 % of 158 patients had a good response to treatment; however, the patients with serum GDF-15 level above 2,720 ng/L demonstrated a significantly higher risk of cardiovascular mortality and rehospitalization due to HF decompensation in 30 months [25].

The study of D. Lok et al. (2013) included the analysis of the levels of NT-proBNP, GDF-15, Gal-3 and troponin in patients with FC III CHF (NYHA). The authors summarized that the GDF-15 biomarker is an indicator with better predictive value compared to NT-proBNP and other analyzed biomarkers [26].

In 2012, Dutch researchers analyzed GDF-15 concentration in the myocardial tissue of patients with non-ischemic dilated cardiomyopathy (DCM). Tissue samples were obtained during implantation of devices that support the left ventricle function or during heart transplantation. A strong statistically significant correlation was found between GDF-15 level and the severity of myocardial fibrosis [27]. One month after implantation of the device, GDF-15 levels were significantly reduced compared to the pre-implantation period; this fact indicates a relationship between the level of the analyzed biomarker and the severity of myocardial dysfunction [27].

O. M. Drapkina (2013) in her study with the participation of 55 patients with HF established a relationship between the GDF-15 biomarker and LV diastolic dysfunction (DD) parameters — peak E/A ratio (according to echocardiography (ECHO-CG)) (r = –0.26); this may represent an additional rationale for the use of GDF-15 as a laboratory diagnostic instrument for HFnEF. The data on a lower concentration of the GDF-15 biomarker in the patients treated with angiotensin II receptor blockers [28] can serve as indirect evidence of the involvement of this biological marker in HFpEF pathogenesis.

According to Ye. V. Bazaeva (2017), the levels of NT-proBNP, GDF-15, Gal-3 and PTX3 have statistically significant diagnostic value only in patients with NYHA FC I–II CHF with reduced LV contractility [29].

We should mention the work performed by Russian researchers that included the analysis of the relationship

of GDF-15 level in blood with ECHO-CG parameters in 34 CHF patients of comparable age with intermediate EF of LV (HFpEF) depending on the presence of myocardial infarction (MI) in their history. In patients without MI, there was a moderate negative correlation between LVEF and GDF-15 concentration ($r = -0.51$, $p = 0.050$), as well as a strong inverse relationship with LV stroke volume ($r = -0.722$, $p = 0.002$). Post-MI patients demonstrated no association between GDF-15 levels and the degree of systolic dysfunction [30].

According to V. D. Sivolap and Ya. V. Zemlyany (2014), the most significant prognostic potential in patients with HFpEF who developed adverse cardiovascular events belonged to the levels of GDF-15 and NT-proBNP, as well as to E/E' value according to ECHO-CG results. In patients with asymptomatic LV diastolic dysfunction, only GDF-15 had the highest prognostic value. In both groups, the combination of these two biological markers increased the predictive value of each of them [31].

In 2018, J. Li et al. (2018) examined 219 HF patients admitted to the Cardiology Department of Tianjin Medical Center and 32 healthy volunteers. Levels of circulating GDF-15, NT-proBNP, pro-collagen type I C-terminal propeptide (PICP) and pro-collagen type III N-terminal propeptide (PIIINP) were determined. All patients were followed up during 12 months. Plasma GDF-15 levels in HF patients were higher than in the control group ($p < 0.05$) and elevated with the progression of the disease ($p < 0.05$). Patients with HFnEF had higher GDF-15 levels compared to patients with HFpEF ($p < 0.05$). GDF-15 level demonstrated positive correlation with LV mass index (LVMI) ($r = 0.433$, $p < 0.05$), PICP ($r = 0.378$, $p < 0.001$), and PIIINP ($r = 0.382$, $p < 0.001$). When plotting ROC curves, the combination of GDF-15 and NT-proBNP (AUC = 0.905, 95% CI: 0.868–0.942, $p < 0.001$) was superior to NT-proBNP (AUC = 0.869, 95% CI: 0.825–0.913, $p < 0.001$) in the diagnosis of HF. Thus, GDF-15 in combination with NT-proBNP significantly improves the accuracy of diagnosing HF [32].

The research performed by American scientists N. Nair and E. B. Gongora is also of interest (2018): they examined 24 patients with DCM and 8 healthy volunteers. Coronary angiography revealed intact coronary arteries in all patients with DCM. Plasma levels of GDF-15, matrix metalloproteinase-2 (MMP2), MMP3, MMP9, tissue inhibitor of MMP 1 (TIMP1), ST2, and BNP were determined. The results of statistical analysis revealed a strong correlation of GDF-15 with TIMP1 ($r = 0.83$, $p < 0.0001$), a weaker one with MMP3 ($r = 0.41$, $p = 0.011$) and MMP2 ($r = 0.47$, $p = 0.003$). MMP9 also demonstrated a weak correlation with GDF-15 ($r = 0.3036$, $p = 0.046$). GDF-15 had negative correlation with the MMP2/TIMP1 ratio ($r = -0.47$, $p = 0.006$); strong correlation of ST2 with GDF-15 was observed ($r = 0.7$, $p < 0.0001$). GDF-15 level correlated negatively with LVEF ($r = -0.49$, $p = 0.004$) and positively with LV end-diastolic size ($r = 0.58$, $p = 0.0006$). GDF-15 demonstrated a significant direct relationship with HF FC (NYHA) ($r = 0.71$, $p < 0.00001$) and BNP concentration ($r = 0.86$, $p < 0.00001$) [33].

A year later, the employees of the Department of Cardiology of the Institute of Clinical and Experimental Medicine-IKEM (Czech Republic) evaluated the role of GDF-15 in patients with heart failure and chronic kidney disease who had estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. As a part of the study, 358 patients with stable systolic HF were followed up for 1,121 days. The authors concluded that GDF-15 in this category of patients had stronger association with adverse outcomes than BNP [34]. Similar evidence was obtained by C. Tuegel et al. (2018) (University of Washington School of Medicine) [35].

A number of studies revealed increased GDF-15 levels in patients with decompensated heart failure (NT-proBNP above 1,200 ng/L); patients with higher levels of the GDF-15 biomarker on admission to the hospital and with its high increase during hospitalization had a high risk of readmissions and mortality after discharge [36, 37].

In a study conducted by M. Boulogne et al. (2017) with the participation of 55 patients with HFnEF, serial measurements of several biomarkers were carried out at the beginning of hospitalization for disease decompensation and after 1 month. Similar trends in the changes of GDF-15 and BNP levels were observed. In this study, a rapid drop in GDF-15 levels was accompanied by apparent clinical improvement in patients. Moreover, the models with the combination of GDF-15 with known and well-studied biological markers such as troponin and BNP have demonstrated that the addition of this parameter increased the predictive value of laboratory biomarkers [38].

In 2020, Tomsk researchers examined 87 patients with nonvalvular atrial fibrillation (AF). All patients underwent general clinical examination, echocardiography, and laboratory tests including fasting blood glucose, creatinine, eGFR, NT-proBNP, highly sensitive CRP, and GDF-15. According to the results of the study, elevated GDF-15 concentrations were associated with age, HF severity and arterial hypertension, increased risk of thromboembolic complications according to the CHA2DS2-VASc scale, impaired carbohydrate metabolism, increased CRP and NT-proBNP levels, increased size of both atria, signs of diastolic LV dysfunction and its remodeling in the form of eccentric hypertrophy [39].

The same year, Austrian physicians conducted a study to investigate the correlation of serum levels of soluble urokinase-type plasminogen activator receptor (suPAR), GDF-15, heart-type fatty acid-binding protein (H-FABP), and ST2 with LVEF in 361 patients with ischemic HF. There was a statistically significant negative correlation between suPAR, GDF-15, H-FABP, and ST2 levels with LVEF. A multiple logistic regression model demonstrated independent relationship between GDF-15 ($p = 0.009$) and NT-proBNP ($p = 0.003$) and LVEF. The authors concluded that in addition to NT-proBNP that is a well-known marker for risk predicting, GDF-15 may be an additional laboratory instrument for the diagnosis and clinical follow-up of patients with HF [40].

Researchers at the University of Bergen conducted a study of a panel of 37 biomarkers to predict adverse cardiovascular events in post-MI patients. The protocol included the analysis of GDF-15, proadrenomedullin (MR-proADM), soluble tumor necrosis factor receptor (sTNFR), C-terminal proendothelin-1 (CT-pro-ET-1), C-terminal telopeptide of type 1 collagen (ICTP), C-terminal provasopressin (CT-proAVP), uric acid, chromogranin A (CGA), and procollagen type III N-terminal propeptide (PIIINP). This group of biomarkers proved to have the strongest predictive value of all-cause mortality and mortality from cardiovascular diseases including that from HF. In multivariate statistical analysis, incremental capacity of laboratory biomarkers was observed even after adjusting for several clinical covariates [41].

In 2021, P. Lourenço et al. examined patients with acute HF and concluded that patients with GDF-15 levels ≥ 3,500 ng/mL on admission to the hospital and ≥ 3,000 ng/mL on discharge were at high risk of death within 1 year [42].

The results obtained by German researchers (K. Nolte et al., 2015) demonstrated that in patients with asymptomatic LV diastolic dysfunction, plasma concentrations of GDF-15, MR-proADM and CT-proAVP were significantly higher compared to the control group. In contrast, the levels of NT-proBNP, MR-proANP, and CT-proET1 showed no statistically significant difference [43].

Ischemic/reperfusion (I/R) injury that inevitably develops during heart transplantation is a major factor leading to organ failure and transplant rejection. To develop novel treatment to prevent I/R injury, both a murine heart transplantation model with 24-hour cold I/R and an in vitro cell culture system were used to determine whether GDF-15 is a protective factor in preventing I/R injury during heart transplantation. Cold I/R was found to cause severe damage to endocardium, epicardium, and myocardium in heart transplants from wild-type C57BL/6 mice, while transplants from GDF-15 transgenic mice showed less damage, as demonstrated by decreased cell apoptosis/death, decreased neutrophil infiltration, and preservation of the normal structure of heart. Overexpression of GDF-15 reduced the expression of the phosphorylated transcription factor RelA p65 and pro-apoptotic genes, while it enhanced the phosphorylation of the Foxo3a gene in vitro and in vivo. Overexpression of GDF-15 inhibited cell apoptosis and reduced neutrophil infiltration. This study first demonstrated that GDF-15 was a promising target for preventing cold I/R injury in heart transplantation. It also demonstrated that the resulting protective effects were mediated by Foxo3 and NF-κB signaling pathways [44].

Conclusion

According to the Framingham study, five-year survival after the onset of clinical HF symptoms is only 25 % and 38 % in male and female patients, respectively [1]. CHF clinical manifestations are not specific enough, and ECHO-CG does not always reveal diagnostically significant changes, so, if CHF is suspected, biological markers in blood can be used as an alternative non-invasive diagnostic instrument. New markers, such as fibroblast growth factor 23, adrenomedullin, fibrosis marker Gal-3, stimulating growth factor ST2, chemokine CX3CL1, vasopressin surrogate marker, and others, are increasingly being used in real clinical practice. Currently, we have advanced technologies for identifying new biomarkers. The next step will be the development of a multi-biomarker model that will require the improvement of bioinformational technologies used for a large database analysis. The potential of this field is enormous not only for the discovery of new diagnostic biological markers, however, also for the improvement of HF treatment.

GDF-15 is a serum biological marker that is expressed due to stress, tissue damage, and inflammation [45]. Unlike other markers of necrosis that have cycles of rise and fall, GDF-15 is relatively stable and causes no particular difficulties in its implementation in clinical practice [46]. GDF-15 concentration in patients with CHF is associated with an increased risk of overall mortality and adverse cardiovascular events; GDF-15 demonstrated prognostic and diagnostic value in patients with HFpEF (Figure 1).

Data from the Framingham Heart Study that included evaluation of 85 biomarkers in 3,523 participants over 14-year follow-up, demonstrated that GDF-15 was the only biomarker in multivariate analysis that was statistically significantly associated with

all adverse cardiovascular events [7]. Pooled data from eight studies including 4,126 patients demonstrated that overexpression of GDF-15 was associated with an increased risk of mortality in patients with HF [47]. In 2019, Chinese researchers reported that GDF-15 was not inferior to NT-proBNP as a prognostic biomarker in patients with acute HF [48].

GDF-15 meets the criteria defined by R. S. Vasan (2006) as a biological marker of increased cardiovascular risk [49]. Table 1 presents the results of the most significant studies of the effect of GDF-15 on CVDs and their outcomes. To confirm the value of determination of blood GDF-15 in patients with HF, additional studies are required.

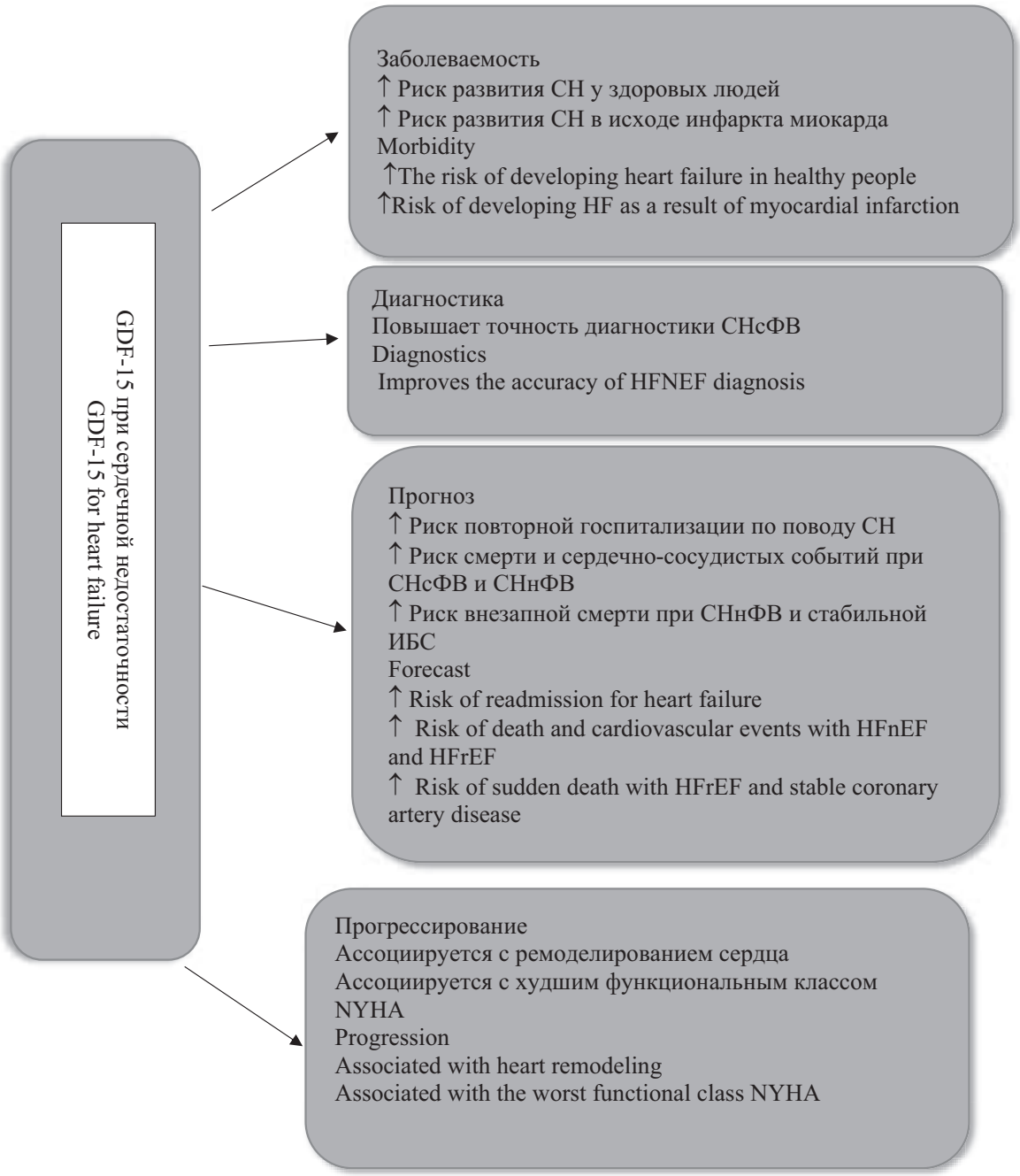

Figure 1. *Relation of GDF-15 to clinical aspects in heart failure*

Legend: HF — heart failure; IHD- ischemic heart disease; HFrEF — heart failure with reduced LV EF; HFnEF — heart failure with normal LV EF; NYHA — New York Heart Association Functional Classification

Table 1. *The most significant studies on the impact of GDF-15 on CVD and their outcomes*

Researchers	Markers	Members	Results
Khan S.Q. et al. [13]	GDF-15, NT-proBNP	• 1142 patients with acute myocardial infarction: 509 with ST elevation myocardial infarction; 633 with non-ST elevation myocardial infarction). • Age 67 (IQR: 24-97) years.	• GDF-15 increased with increasing Killip class (p <0,001) and correlated with NT-proBNP (r=0,47, p < 0,001). • AUROC for predicting death and HF: GDF-15 — 0,73, NT-proBNP — 0.76, combination of biomarkers — 0,81.
Anand I.S. et al. [14]	GDF-15	• 1734 patients from the Val-HeFT study (the efficacy of Valsartan in patients with heart failure) • Age 67 (IQR: 24-97) years • NYHA III and IV FC — 43 %	An increase in GDF-15 of 100 ng/L over 12 months has been associated with an increased risk of: • death by 1.7 % (HR: 1,017; 95 % CI 1,014 — 1,019; p <0.001) • the first pathological event (CPR, hospitalization for heart failure, inotropic support) by 2,0 % (HR: 1,020; 95 % CI 1,017 — 1,023; p <0,001)
Xie S. et al. [16]	GDF-15	Metaanalysis: • 31 studies (53706 subjects with 7020 adverse outcomes (MI, HF, death). • Follow-up for at least 3 months. • Average age ranged from 42 to 79 years	As GDF-15 increased, the risk of adverse events increased: • CVD mortality (HR: 2,11; 95 % CI, 1,57–2,66), • all-cause mortality (HR: 2,70; 95 % CI, 2,29-3,12), • adverse outcome (RR: 1.96; 95 % CI 1.64–2.29).
Sinning C. et al. [18]	sST2, GDF-15, NT-proBNP СРБ	5,000 people from the Grutenberg Population Health Study (randomly selected): • 2460 women (mean age 55 years • 2540 men (mean age 56)	• AUROC for the diagnosis of CHF -GDF-15 — 0,79, NT-proBNP — 0,77, CRP — 0,66, sST2 — 0,62 • in addition to NT-proBNP improved detection of HF (OR: 1,4, 95 % CI: 1,1-1,7) • The best biomarkers for predicting all-cause mortality were NT-proBNP (HR: 1,9, 95 % CI: 1,6–2,2; p <0.001) and GDF-15 (HR: 1.7, 95 % CI: 1,6–1,9, p <0,001)
Bouabdallaoui N. et al. [24]	GDF-15	• 1935 patients with NYHA II–IV HF, elevated BNP or NT-proBNP, SDLV (EF≤40 %) from the PARADIGM-HF study (RCT on the effect of ARNI on CVD death and hospitalization for HF). • Mean age 67 ± 10 years	An increase in GDF-15 at each point (baseline, 1 and 8 months later) of 20 % was associated with a higher risk of: • mortality (HR: 1,13, 95 % CI 1,08-1,18, p <0.001), • hospitalizations for heart failure and cardiovascular events (HR: 1,09, 95 % CI 1,05-1,14, p <0,001), • death from heart failure (HR: 1,16, 95 % CI 1,05-1,28, p <0,001)
Bonaca M. et al. [46]	GDF-15	• 3501 post-ACS patients (~day 7) from the PROVE IT-TIMI 22 trial to investigate the efficacy of standard or intensive statin therapy. • Follow-up period 2 years. • Mean age 58,1 ± 11.1 years	• At established thresholds, GDF-15 (<1200, 1200-1800, and >1800 ng/L) were associated with a 2-year risk of death or MI (5,7 %, 8,1 %, and 15,1 %, respectively; p <0,001) • GDF-15 was associated with risk of death or MI (adjusted RR per unit increase in GDF-15: 2,1, 95 % CI, 1,6–2,9; p <0,001)

Legend: ACS — acute coronary syndrome ARNI — angiotensin receptor and neprilysin inhibitor; AUROC — area under the ROC curve; BNP — brain natriuretic peptide; CI — confidence interval; CPR — cardiopulmonary resuscitation; CRP, C-reactive protein; CVD — cardiovascular diseases; CVE — cardiovascular events; EF — ejection fraction; GDF-15, growth differentiation factor 15; HF — heart failure; HR — Hazard ratio; MI STEMI — myocardial infarction with ST segment elevation; ; SDLV — systolic dysfunction of the left ventricle; NT-proBNP — N-terminal pro-brain natriuretic peptide; STEMI — myocardial infarction without ST segment elevation; sST2 — soluble tumorigenicity suppression receptor type II

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ЭТИОЛОГИЧЕСКАЯ СТРУКТУРА ИНФЕКЦИОННОГО ЭНДОКАРДИТА У ОТДЕЛЬНЫХ КАТЕГОРИЙ ПАЦИЕНТОВ (ОБЗОР ЛИТЕРАТУРЫ)

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Etiological Structure of Infective Endocarditis in Certain Categories of Patients (Literature Review)

Резюме

В обзоре представлена информация о наиболее частых возбудителях инфекционного эндокардита (ИЭ) среди отдельных категорий пациентов. Основываясь на анализе современных отечественных и зарубежных источников, посвященных изучению ИЭ, в статье описываются условия, предрасполагающие к доминированию тех или иных микроорганизмов у потребителей инъекционных наркотиков, ВИЧ-инфицированных пациентов, пациентов на гемодиализе, с клапанными протезами, пациентов с сахарным диабетом, злокачественными новообразованиями, пожилых пациентов и у беременных.

Рассматривается распределение как типичных для ИЭ (стафилококки, стрептококки, энтерококки), так и редких микроорганизмов, а также полимикробного эндокардита в перечисленных группах. Обсуждаются возможные причины преобладания метициллин-чувствительных или метициллин-резистентных штаммов *Staphylococcus aureus* у разных категорий пациентов с ИЭ, развития заболевания, инициированного редкими для него формами микробных агентов у пациентов с ослабленным иммунитетом, особенности микробной флоры в зависимости от сроков развития клапанной инфекции после протезирования. Несмотря на представления о преобладании того или иного микроорганизма как возбудителя ИЭ в конкретной клинической ситуации, при оказании помощи таким пациентам следует стремиться к точной верификации этиологического фактора для выбора эффективной антибактериальной терапии.

Ключевые слова: *инфекционный эндокардит, этиология, внутривенные наркоманы, ВИЧ-инфицированные, пожилые, беременность, сахарный диабет, злокачественные опухоли, гемодиализ, инфекция протезированных клапанов*

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Abstract

The review contains information about the most common pathogens of infective endocarditis (IE) in certain categories of patients. Basing on analysis of current national and foreign sources concerning IE study there are description of conditions favoring to dominance of various microorganisms in intravenous drug users, HIV-infected patients, patients on hemodialysis, with valve prostheses, diabetes mellitus and malignant neoplasm patients, elderly patients, and pregnant women.

Distribution of both as typical for IE (*staphylococci, streptococci, enterococci*) and rare microorganisms as well polymicrobial endocarditis in mentioned above groups is considered. There is discussion about possible reasons of prevalence of methicillin-sensitive or methicillin-resistant *Staphylococcus aureus* species in different IE patient categories, disease development initiated by rare forms of microbial agents in immunosuppressive patients, microbial flora features depending on terms valvular infection after valve prosthetics. Despite on consideration about predominance of one or another microorganism as an etiologic agent of IE in given clinical situation, during medical help providing it should strive for precise verification of an etiologic factor for choice of effective antibacterial treatment.

Key words: *infective endocarditis, etiology, intravenous drug users, HIV-infected, elderly, pregnancy, diabetes mellitus, malignant tumors, hemodialysis, prosthetic valve infection*

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ART — antiretroviral therapy, DM — diabetes mellitus, HIV — human immunodeficiency virus, HD — hemodialysis, IDU — injecting drug user, IE — infective endocarditis, PVIE — prosthetic valve infective endocarditis

Introduction

Infective endocarditis (IE) is a relatively rare (incidence in general population ranges from 1.5 to 11.6 cases per 100,000) and, at the same time, rather severe disease with a persistently high level of hospitalization (6.9–20.0 %) and annual mortality rate (up to 40 %) [1]. The main causes of poor outcome include severe valvular dysfunction, thromboembolic complications, sepsis, and multiple organ failure. IE course in each case depends on several factors: specific features of the causative agent of the disease, underlying diseases and comorbidities, the presence of immunodeficiency, and potential genetic predisposition in certain patients [1, 2]. Obviously, the properties of the causative agent (various pathogenic power and virulence factors, massive infection and route of entering the bloodstream, resistance to antibiotics) largely determine the clinical scenario of IE, and the fight against an infectious agent, i.e., reasonable antibacterial therapy remains the main line of the management of this disease in the 21st century. Detection of etiology based on the results of bacteriological, less often — of serological blood tests is a major diagnostic criterion for IE indicated in international consensus documents [3, 4]. However, in real-life clinical practice, one often has to start empirical antibiotic treatment for IE (prior to getting the results of blood culture, or if they are negative) [5, 6] assuming the most likely pathogen in a particular case. In such cases, the most correct assumption of a probable etiological factor based on the assessment of medical history and clinical setting can significantly help in choosing the optimal empirical antibiotic therapy regimen, therefore, it can have a positive effect on the disease outcome [7].

The etiology of IE has undergone certain changes since the first bacteriological study performed at the end of the 19th century [8]. Thus, streptococci, being the “leaders” of the infectious process in IE at the end of the 19th — early 20th century, gave way to

staphylococci [9]. However, IE still remains predominantly a gram-positive infection with the leading etiological role of staphylococci, streptococci, and enterococci [2]. The changes in the etiological structure of IE are associated with the increased number of invasive diagnostic and therapeutic procedures: cardiac surgeries, implantation of pacemakers, hemodialysis, as well as intravenous administration of drug products and narcotic drugs [2].

Patients with diabetes mellitus (DM), individuals infected with the human immunodeficiency virus (HIV), and patients taking drug products that suppress their immune system (for example, for autoimmune, malignant diseases, organ transplantation, etc.) are at the highest overall (non-cardiac) risk of IE. This review provides up-to-date information on the most likely causative agents of the disease in certain groups of patients, in particular, in injection drug users, HIV-infected patients, patients on hemodialysis, patients with DM, malignant neoplasms, as well as in pregnant women and the elderly.

The Role of Microbiology Testing in the Diagnosis of Infective Endocarditis

Since 2000, the diagnosis of IE is based on the Modified Duke Clinical Diagnostic Criteria (developed at Duke University, Durham, USA) that were extended with the detection of *S. aureus* in blood culture, regardless of the route of infection, as well as with bacteriological and/or serological evidence of *Coxiella burnetii*, and results of transesophageal echocardiography (Table 1) [3].

A positive result of blood culture is one of the two major diagnostic criteria for IE, therefore, the identification of the causative agent is the most important step in diagnosis and a reliable parameter for choosing an adequate antibacterial drug. Blood culture allows identifying the pathogen and checking its sensitivity to antibiotics.

The absence of culture growth during routine microbiological test suggests that the etiological factor includes pathogens that are rarely associated with endocarditis.

Table 1. *Modified Duke criteria with 2015 ESC additions [4].*

Major criteria
Blood culture positive for IE
a. Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus* **or** • community-acquired enterococci, in the absence of a primary focus **or**
b. Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: • at least 2 positive cultures of blood samples drawn 12 h apart **or** • all of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart) **or**
c. Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer 11 : 800
Imaging methods are positive for IE
a. Echocardiogram positive for IE • vegetation • abscess, pseudoaneurysm, intracardiac fistula • perforation or valve aneurysm • new partial dehiscence of prosthetic valve.
b. *Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.*
c. *Definite paravalvular lesions by cardiac CT.*
Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever as temperature >38°C.
3. Vascular phenomena *(including those detected by imaging only)*: major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

The diagnosis of IE is considered definitive if:	**The diagnosis of IE is considered possible in the presence of:**
2 major criteria **or**	1 major criterion and 1 minor criterion **or**
1 major criterion and 3 minor criteria **or**	3 minor criteria
5 minor criteria	

Note: additions of the European Society of Cardiology are in italics [4]
^{18}F-FDG — fluorodeoxyglucose; HACEK — *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*; IE — infective endocarditis; CT — computed tomography; SPECT — single photon emission computerized tomography; PET — positron emission tomography

These may be, for example, non-toxigenic, extracellular bacteria that require complex feed conditions for their growth in laboratory, as well as fungal flora or intracellular pathogens (in particular, *Coxiella burnetii, Chlamydia, Tropheryma whipplei*) that cannot be identified in routine clinical practice [10].

To identify these microorganisms, an extended bacteriological test is recommended, including blood culture on chocolate agar, as well as serological, immunological, and immunohistochemical methods. The results of polymerase chain reaction in blood tests and of the resected surgical material of valve tissue or embolic fragments are extremely important [11].

Etiology and Special Aspects of the Pathogenesis of Infective Endocarditis in General Population

Among the causative agents of IE, coccal flora is prevailing: staphylococci and streptococci cause 70–80 % of cases [12]. *S. aureus* remains the predominant pathogen that causes IE in 25–30 % of cases, while the proportion of coagulase-negative staphylococci is 8–11 % [12]. Streptococci, mainly of *Viridans* group, cause the disease in about 30 % of cases. Gram-negative microorganisms, including those of HACEK group (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella* subspecies), are the causative agents of IE in 3–5 % of cases; much less often this disease is caused by non-HACEK pathogens, such as *Escherichia coli, Pseudomonas aeruginosa*, *Klebsiella* strains, *Serratia, Proteus mirabilis, Stenotrophomonas maltophilia, Enterobacter cloacae*, etc. [10].

Fungal flora rarely (up to 2 %) serves an etiological factor for IE and is found mainly in immunosuppressed patients [5].

According to the present-day concept, microbial vegetation development starts with the entry of bacteria into systemic flow via oral cavity, gastrointestinal or urogenital tract, or skin (microtrauma, pustular infections), venous catheters, or after invasive diagnostic or surgical procedures. Bacteremia, being the first stage in pathogenesis events, initiates the subsequent ones, namely, adhesion and colonization [13]. During the second stage, i.e., adhesion, bacteria (especially gram-positive ones) attach to abnormal or damaged endothelium with the help of surface adhesins [13]. These specific proteins act as mediator of bacterial adhesion to host extracellular matrix proteins; this process is facilitated by platelet microthrombi and fibrin. Finally, bacterial adhesion promotes the growth of the colonies of microorganisms when bacterial reproduction takes place simultaneously with the migration of white blood cells, infiltration, and inflammation that result in the development of a mature vegetation [14]. Biofilm that can be produced by most of the microorganisms that cause IE protects them against the host immune response. This protective mechanism allows a bacterial cluster entering the extracellular mucus-like matrix with quorum sensing and synchronization of gene expression that accelerates the development and maturation of vegetation [14].

Infective Endocarditis in Intravenous Drug Users

The problem of the illegal use of drugs remains relevant in today's context. According to the international report [15], in 2019, a total of 275 million people used illegal drugs; this value is 22 % higher compared to the year 2010. The number of injection drug users is over 11.0 million (range 8.9 to 14.2 million) [15]. The most severe bacterial complications in injection drug users (IDUs) are endovascular infections, including IE, with the incidence in this category of patients 8.0–37.8 % of the total number of cases [16].

Conditions for bacteremia development in IDUs include: infections of skin and soft tissues; using saliva as a solvent for a narcotic substance; injections in non-sterile conditions, and the repeated use of devices for the preparation of injected drugs [17]. IDUs are the risk group for developing IE due to frequent comorbidities that have an immunosuppressive effect (HIV infection, hepatitis C). The abovementioned characteristics of such patients results in the high incidence of IE that is almost 20-fold compared to the general population (1.5 to 3.3 cases per 1,000 IDUs per year) [16].

IE in IDUs differs from that in general patient population. The disease is more common in young patients [18]; damage to the right heart is known to be predominant (up to 76–90 % of cases) with the development of severe complications: sepsis, heart failure (HF), and embolism [19]. In addition, there are cases of IE in injecting drug users with and atypical course — without fever [20].

Like in general population, *S. aureus* is the microorganism that most often causes IE in IDUs (up to 77.2 % of cases of IE in drug users vs 39.6 % in the patients in general population) [8, 21, 22]. It is associated with higher skin colonization by *S. aureus* (probably due to the frequent damage of its integrity) in IDUs compared to the individuals who use drugs only orally. Damage of skin with a needle provides a direct entry of microorganisms into the bloodstream. Papers with the analysis of the disease in IDUs published in recent years describe the prevalence of the methicillin-sensitive strain of *S. aureus* over the methicillin-resistant one [18, 21–23]. W. Lorson et al. (2019) emphasize the etiological significance of the methicillin-resistant strains of *S. aureus* and

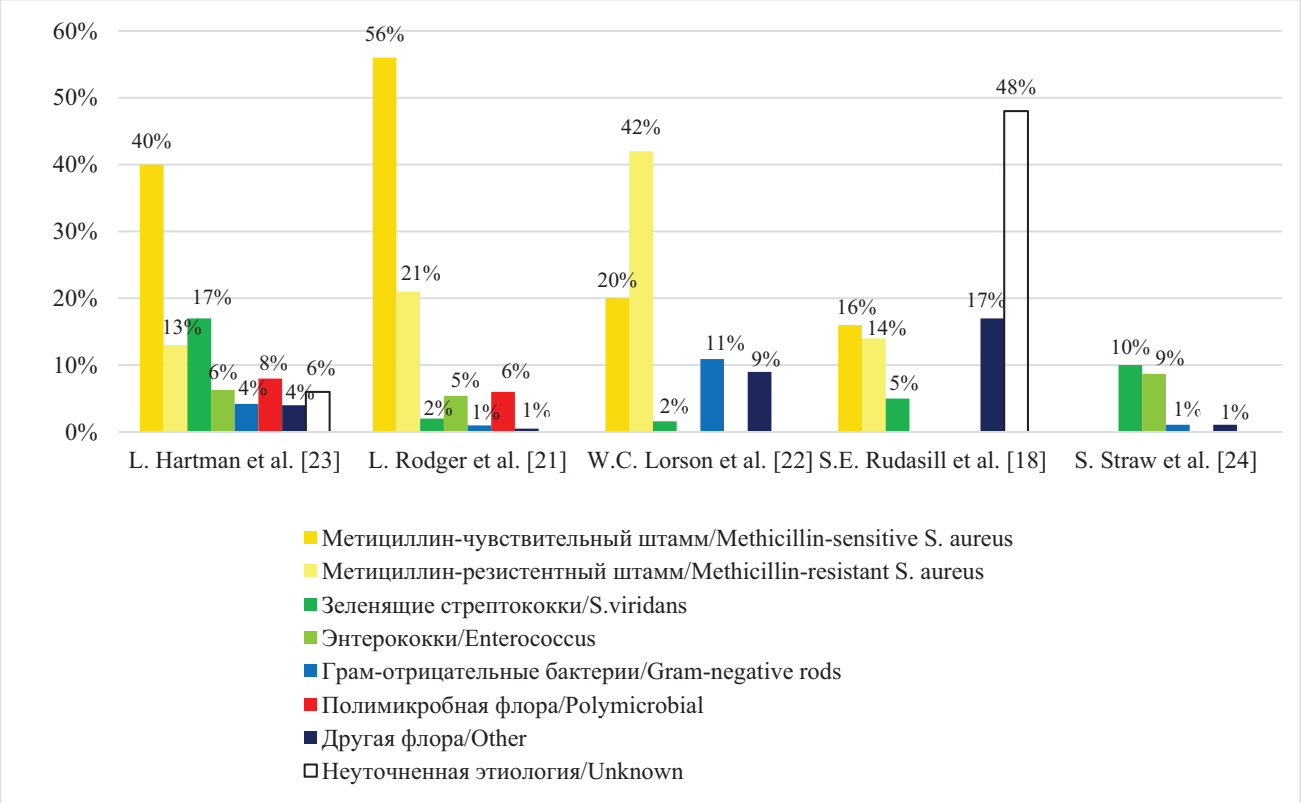

Figure 1. *The etiological structure of infective endocarditis in injection drug users*

Pseudomonas in the development of IE in IDUs, as well as the need to use antibiotics that are active against these pathogens [22].

Streptococci can also be an etiological factor for IE in IDUs. Detection rate of the bacteria of streptococcus group (*Viridans* group, enterococci, other streptococci) in the analyzed works ranged from 2 to 20 % (Figure 1) [18, 21–24].

Streptococcus pyogenes or group A *streptococcus* were previously considered to be relatively rare causative agents of IE both in general population and in IDUs. However, M. Rebechi et al. in their report (2021) mentioned the increased number of IE cases caused by *S. pyogenes* or group A *S.*; 16 (89 %) out of 18 patients with IE of the indicated etiology took injection drugs [25].

In addition to staphylococci and streptococci, IE in IDUs can be caused by rare causative agents with a higher incidence of pseudomonas, fungal strains, and polymicrobial combinations [26].

Polymicrobial endocarditis is rare, however, it is characterized by high mortality, especially in cases when the combination of microorganisms includes the representatives of *Candida* family [26]. The most common is the combination of *S. aureus* and *S. pneumoniae*; the second most frequently described combination is *S. aureus* and *Pseudomonas aeruginosa* [22]. Polymicrobial endocarditis has been described particularly in IDUs; it is often accompanied with the damage to several heart valves [26]. Management of such patients is associated with significant difficulties, primarily due to resistance to common combinations of antibacterial drugs. Chances of a favorable disease outcome can be increased only with a combination of long-term intravenous administration of antibiotics in combination with antifungal drugs, and, if necessary, with timely surgical treatment [26].

Using saliva as a solvent for intravenous drug injections may cause the growth of conventionally nonpathogenic organisms in IDUs with IE, such as *Haemophilus parainfluenzae, Eikenella corrodens* and *Streptococcus miller* [16, 17].

Obviously, if the right heart is affected and there is evidence or suspicion of intravenous drug use, or if a venous catheter is placed, then the initial choice of empiric antimicrobial therapy is aimed to manage *S. aureus.*

Etiology of Infective Endocarditis with Underlying HIV Infection

Analysis of the etiological aspect of IE in this category of patients requires considering both the aspect of intravenous drug use and the state of immune system, including the presence/absence of antiretroviral therapy

(ART). IE in patients with HIV infection is uncommon [4], predominantly in IDUs [27]. Therefore, staphylococci are the prevailing etiological factor in this group of patients [4]. A certain etiological role in IE development in the setting of immunosuppression belongs to pathogenic yeast fungi (especially with the intravenous administration of heroin dissolved in lemon juice) and gram-negative flora [4, 22]. In HIV patients at the AIDS stage, especially in the absence of ART, there is increased etiological significance of other microorganisms that are not actual causative agents of IE in patients without immunosuppression. For example, there are case reports of Salmonella IE at the late stages of HIV/AIDS in the absence of ART in patients with diarrhea caused by simultaneous intestinal damage by cytomegaloviruses [28]. Enterococcal IE in non-IDU patients with advanced HIV infection was also attributed to severe bowel disease [28]. The probability of enterococcal IE is increased in HIV patients who receive frequent repeated courses of antibiotics to prevent and manage various infections that inhibit the growth of other microorganisms [8, 28]. Less common or rare etiological factors include *Pseudomonas spp.*, *Xanthomonas maltophilia*, *Neisseria spp.*, *Corynebacterium spp.*, coagulase-negative staphylococci, mature *Erysipelothrix*, *Gemella morbillorum, Citrobacter spp., Haemophilus spp.,* and *Eikenella corrodens* [22]. Finally, about 5 % of IE cases are caused by a polymicrobial infection [28].

Infective Endocarditis in Hemodialysis Patients

All patients on renal replacement therapy are at risk of infections, including IE. Predisposing conditions include the specific aspects of a particular method: hemodialysis (HD) requires repeated access to the vascular system through an intravenous catheter or a permanent arteriovenous fistula that leads to frequent episodes of bacteremia; peritoneal dialysis requires a dialysis catheter placed in abdominal cavity; kidney transplantation involves lifelong immunosuppressive therapy. Another risk factor for IE development of heart valve calcification in patients with end-stage renal disease [29] that is caused by the disorder of calcium and phosphorus metabolism with underlying secondary hyperparathyroidism and chronic inflammation.

The source of bacteremia that is often observed in patients on long-term HD (in more than 70 % of cases with a central line catheter) [30] can be both endogenous (opportunistic skin flora) and exogenous foci of infection (hands of medical personnel, equipment).

Opportunistic skin pathogens and *S. aureus* are the main causes of vascular access-associated bacteremia in patients who receive long-term HD (up to 75 % of cases) [30, 31]. Other bacteria that cause IE in patients on renal replacement therapy include coagulase-negative staphylococci, *Streptococcus* group, *Enterococcus* group, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa* [30, 31].

Over the recent years, the increased incidence of methicillin-resistant *S. aureus* strains is observed in HD patients; according to different authors this value amounts up to 40 % of IE cases [31]. *Candida* species are found extremely rarely. At the same time, the results of blood culture tests are quite often negative; this fact is most often associated with the previous use of antibacterial agents that significantly complicates the following treatment [32].

H. Jeon et al. in their paper (2020) analyzed the relationship between the type of vascular access (temporary/catheter or permanent access) and the route of infection in patients who underwent the HD procedure and were hospitalized with a diagnosis of IE (96 individuals) [33]. Fifty-seven of them had a permanent dialysis catheter. A hemodialysis access site was in most cases (82 %) identified as the main source of infection. The most common causative agent of endocarditis in both the catheter access group and the permanent access group was methicillin-susceptible *S. aureus* that was the cause of the disease in more than a third of cases. More cases of enterococcal endocarditis were observed in the catheter access group than in the permanent access group (27 % vs 8 %, p = 0.03). A total of 4 cases of IE caused by vancomycin-resistant enterococci were reported.

Native Valve Infective Endocarditis in Patients with Diabetes Mellitus

Studying the specific features of IE in patients with DM is required primarily due to the significant number of such patients and the increasing prevalence of DM throughout the world. According to the World Health Organization, 422 million people had diabetes in 2014; moreover, this value has tripled since 1980 [34]. Observed population aging and generally increasing incidence of obesity will obviously contribute to the currently growing DM morbidity rate. Immune dysfunction in patients with DM contributes to the development of infectious complications, including sepsis and IE. In addition, patients with DM are prone to severe endothelial dysfunction that is one of the main pathogenetic stages in the development of IE. DM has been actually identified as a risk factor for poor prognosis in various bacterial infections, including IE [35].

The high prevalence of DM in patients with IE is confirmed by recent large-scale studies performed by

T. Abe et al. (USA) [36] and J. De Miguel-Yanes et al. (Spain) [37]. During analyzing the specific features of IE with underlying DM, the authors of these two researches also compared the etiological structure of the disease in groups of patients with and without concomitant DM.

Patients in the DM group in the Spanish analysis predominantly had such microorganisms as *S. aureus* (14.7 % vs 13.2 %; p = 0.07) and enterococci (16.2 % vs 14.2 %; p = 0.02), while *Viridans streptococci* (18.9 % vs 21.8 %; p = 0.003) were found more often in the patients without concomitant DM [37].

A similar distribution of IE causative agents was found in the analysis carried out by American researchers. Patients with DM more often had *S. aureus* (35.6 % vs 33.1 %; p < 0.001), other staphylococci (6.7 % vs 5.4 %; p < 0.001), enterococci (7.6 % vs 6.5 %; p < 0.001), group B streptococci (1.6 % vs 1.3 %; p < 0.001), and gram-negative organisms (4.8 % vs 3.8 %; p < 0.001) [36].

The authors conclude that the reason for the higher detection rates of staphylococci, enterococci and gram-negative microorganisms may include more frequent hospitalizations of patients with DM for various reasons that contribute to the development of hospital-acquired infections. The high probability of infection with *Staphylococcus aureus* is one of the reasons for poor clinical outcomes in patients with DM and IE, due to the tendency to abscess development and valve destruction that require aggressive antibiotic therapy and early surgical treatment [36].

Infectious Endocarditis in Pregnant Women

Knowledge about IE during pregnancy is limited by the extremely low prevalence of the disease in this group (≈1 case of IE per 100,000 pregnant women) [38]. As a rule, the disease develops secondary to a pre-existing lesion of the cardiac valvular apparatus that may be congenital, less often — rheumatic, or due to intracardiac foreign bodies, or intravenous drug use. As in the general population of non-pregnant patients with IE, there is increased number of reported cases of IE in pregnant women associated with intravenous drug use [38, 39].

Despite the low incidence of IE during pregnancy, maternal mortality amounts to 33 %; in addition, pregnant women with IE have a high incidence of embolic complications and mycotic aneurysms [39]. An erroneous interpretation of several nonspecific symptoms of intracardiac infection (tachycardia, shortness of breath) as hemodynamic changes that are common during pregnancy often makes it difficult to diagnose IE and to start antibiotic therapy timely [40].

In a systematic review of the cases of IE in pregnant and postpartum women, K. Kebed et al. (2014) analyzed maternal risk factors, microbiological profile, as well as both maternal and fetal outcomes [39].

Ninety cases of IE were identified in pregnant and postpartum women. The most frequently detected causative agents were streptococci and staphylococci in 39 (43.3 %) and 23 (25.6 %) women, respectively. Results of culture tests were negative in 8 women (8.9 %), and polymicrobial IE was found in 3 (3.3 %) women.

Localization of IE in the left heart (43 cases with localization on one valve and 6 cases with damage to two valves) was more often observed with streptococcal causative agents compared to staphylococcal ones.

According to the results of the analysis of literature sources for 15 years (1997–2013), S. Yuan has analyzed 30 cases of IE in pregnant women at different periods of pregnancy [41]. Among them, one or two pathogens were found in blood culture or vegetation culture tests in 21 patients. According to the conclusions made by the author, the predominant infectious agent in pregnant women with IE was *Staphylococcus aureus* (38.1 %), the second most common was *Streptococcus viridans* (19 %). The following microorganisms were obtained in culture tests with the same frequency (9.5 %): *S. mitis, S. aureus* with *H. parainfluenzae*, group A α-hemolytic streptococci, *S. agalactiae, S. mutans* with *S. sobrinus, S. sanguis, Salmonella typhi*, and *H. parainfluenzae*. In general, in the study performed by S. Yuan, different species of streptococci caused 48 % of IE cases. *Staphylococcus aureus*, alone or in combination, was isolated in 9 (43 %) cases of IE.

IE of tricuspid valve during pregnancy and after abortion is more often caused by group B streptococci. These bacteria can be isolated from the genital area in 5–40 % of women and also cause the development of neonatal sepsis, chorioamnionitis, endometritis, and maternal bacteremia. Endocarditis in pregnancy is sometimes caused by rare microorganisms. In particular, there are case reports of IE with the following infective agents: *Bacillus cereus, Abiotrophia defectiva, Staphylococcus lugdunensis, Candida parapsilosis*, etc. [41].

Infectious Endocarditis in Elderly Patients

Over the past 50 years, there has been a definite trend towards the increasing incidence of IE in elderly patients [42]. The incidence of IE in people 70+ in different countries is 14.5–20.0 cases per 100 thousand people per year [2, 42].

Specific features of IE etiology in the elderly are due to several characteristics that are typical to this age group. Year by year, we observe the increasing number of elderly patients with prosthetic valves, with hospital-acquired infection due to frequent hospitalizations

and invasive examination methods [2]. About half of all cases of hospital-acquired IE in elderly patients are associated with intravascular catheters and other invasive devices.

Malignant neoplasms, DM, and pathologies of urogenital and digestive tracts are more common in elderly patients [43].

Summarizing the results of studies evaluating the characteristics of IE causative agents in elderly patients (> 65–70 years) compared with younger patients, one should mention the increased frequency of detection of enterococci, *S. bovis*, as well as the relatively decreased number of endocarditis cases caused by *S. viridans*, as well as by *S. aureus* (Figure 2) [42].

Methicillin-resistant and coagulase-negative strains prevail among the staphylococci that are most commonly associated with nosocomial IE [51, 52].

Increased incidence of IE in elderly patients that is caused by enterococci is associated with a higher incidence of inflammatory and oncological diseases of the colon, as well as with frequently performed instrumental procedures for urological and gastrointestinal tracts. IE caused by *S. bovis* is also most commonly associated with neoplastic diseases of large intestine [53].

Elderly patients typically develop IE as a result of the overlay of a hospital-acquired infection that is mainly represented by *S. aureus*. Percutaneous procedures most often cause the development of staphylococcal IE, and procedures on urinary tract — the enterococcal one [4]. Besides, various types of oral streptococci also belong to the causative agents of endocarditis.

As a rule, a prosthetic valve IE demonstrates coagulase-negative oxacillin-resistant staphylococcus in the results of a culture test.

Patients with IE who are in nursing homes often have microorganisms that are resistant to antibiotics: methicillin-resistant staphylococci, vancomycin-resistant enterococci, as well as penicillin-resistant pneumococci [52].

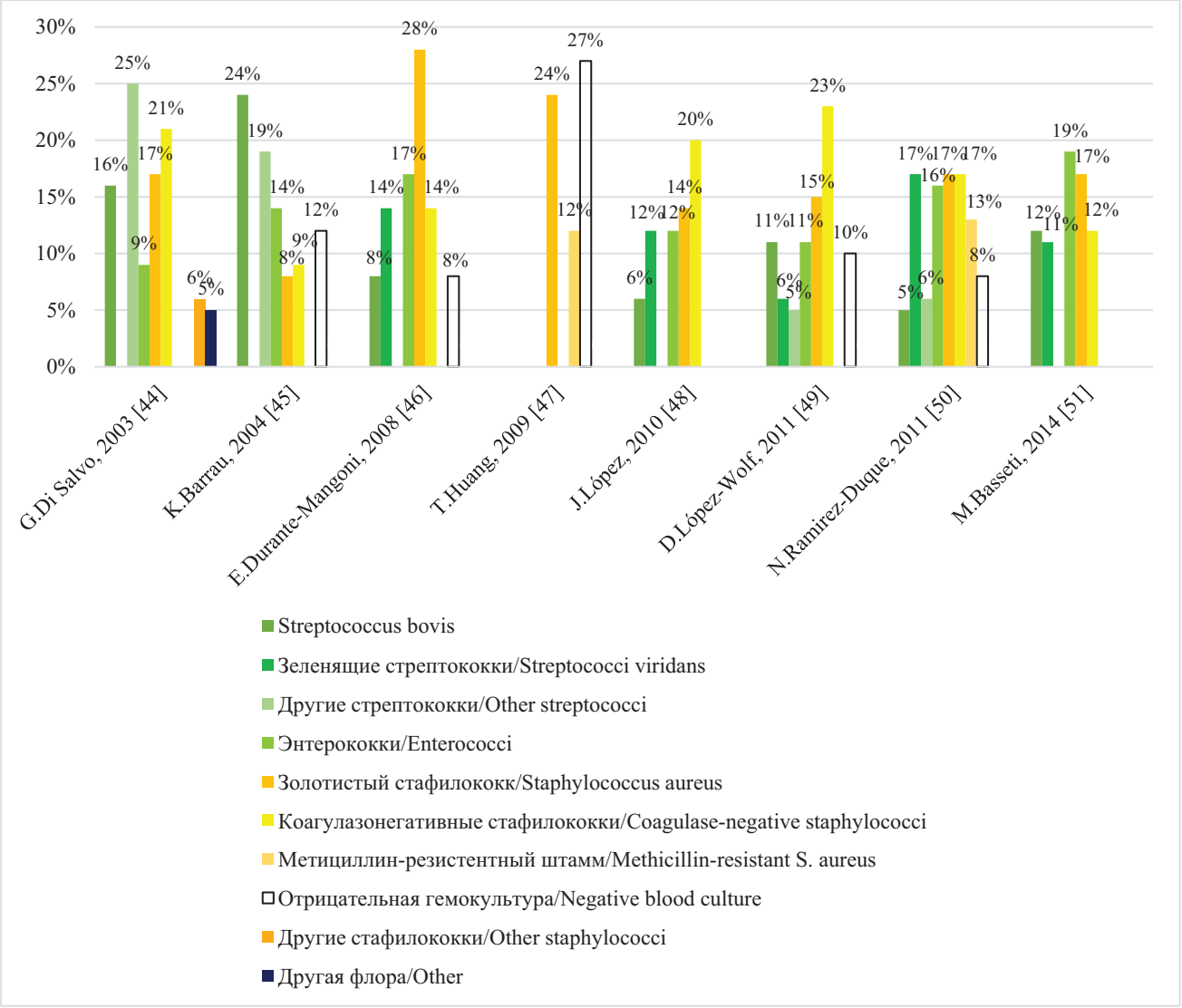

Figure 2. *Characterization of causative agents of infective endocarditis among the elderly*

Gram-negative rods and fungal flora are most commonly found in patients on parenteral nutrition. Causative agents of HACEK group, as well as fungi, are found relatively rare, in 1–5 % of cases [42]. Quite often (8–27 %) one cannot identify the causative agent of the disease [4].

Infective Endocarditis and Malignant Neoplasms

The problem of IE associated with malignant neoplasms is currently of considerable interest due to both increased incidence of IE in elderly patients and increased incidence of malignant tumors in this category of patients [54]. According to the 2015 European Society of Cardiology guidelines, IE in cancer patients is defined as a special type of this disease [6]. Depending on the "mode of entry" of the infection and the clinical situation, the combination of IE with cancer results in bacteremia both with causative agents that are typical for IE (*S. mitis, S. gallolyticus*, other group D streptococci, enterococci, *S. aureus*) and with microorganisms that are rarely found in IE patients (*Lomentospora prolificans*) [54]. Discussed mechanisms that can explain IE development along with neoplasms include bacteremia (a consequence of tumor decay, increased mucosal permeability after frequent invasive medical and diagnostic procedures); immunosuppression induced by chemotherapy and radiation therapy; development of non-bacterial thromboendocarditis caused by hypercoagulation; and age-related changes (marantic endocarditis) [54]. Patients with past IE have the increased probability of malignant tumors, in particular, colorectal cancer and hepatocellular carcinoma that persists for several years [55]. Cases of IE were described in patients with lymphoproliferative diseases, lung, breast and prostate cancer. However, IE develops more often in patients with tumor lesions of colon and rectum than in patients with cancer of other localizations, notably, with a proven etiological importance of *Streptococcus bovis/gallolyticus*. The association of the specified etiological factor of IE in elderly patients with intestinal malignant neoplasms allows considering IE caused by *Streptococcus bovis/gallolyticus* as a marker of a possible oncological pathology with a recommendation for repeated colonoscopy to detect an intestinal tumor both during IE period and in subsequent years [56].

Prosthetic Valve Infective Endocarditis

Prosthetic valve IE (PVIE) develops in 2–10 % of patients during the first year after prosthetics with an incidence of approximately 0.5 % per year in subsequent years; more often — after aortic valve replacement; it equally affects mechanical and biologic prostheses [4]. Early onset of PVIE (especially earlier than 2 months after surgery) is caused by surgical infection with antibiotic resistant bacteria (*S. epidermidis*, diphtheroids, coliform bacilli, *Candida*, *Aspergillus*) or by infection through vascular access devices in the early postoperative period (*S. aureus*) [4]. Late development of PVIE, especially later than 12 months from the day of surgery, is caused mainly by the episodes of transient bacteremia during medical interventions. Microbial flora in late PVIE is almost identical to that in that cases of native valve IE (streptococci, *S. epidermidis,* diphtheroids, gram-negative flora species *Haemophilus*, *Actinobacillus actinomycetemcomitans*, and *Cardiobacterium hominis* [4, 57]. Mortality in patients with prosthetic endocarditis caused by *Staphylococcus aureus* and fungal flora reaches 70 %; survival is significantly higher in patients who underwent surgical removal of affected and infected valves with debridement of the affected areas and prosthesis replacement [58]. PVIE caused by *Pseudomonas aeruginosa* and multidrug-resistant enterococci demonstrates poor response to drug treatment [57]. Generally, the diagnosis of PVIE requires advanced methods of cardiac imaging, and indications for cardiac surgery are determined by the Endocarditis Team [4]. Patients with valve prostheses are at the highest risk of IE development and require antibiotic prophylaxis before invasive medical procedures [4, 14].

Conclusion

Today, in the 21st century, IE remains predominantly a gram-positive infection; staphylococci, streptococci, and enterococci are the "leaders" in a wide range of pathogens that can cause IE. This is evidenced by the analysis of IE etiology both in general patient population and in certain categories of patients. Gram-negative, anaerobic, and fungal flora are defined as the causative agents of IE with a significantly lower frequency. Specific etiological aspects of IE in different groups of patients are determined to a large extent by the massive infection and the route of entering of the causative agent into patient's body. Analysis of a possible source of bacteremia should become an important algorithmic part of the medical records for patients with IE (previous medical procedures and interventions, infectious diseases of skin and soft tissues, nasopharynx, state of teeth and oral cavity, permanent vascular access devices, heart foreign bodies, repeated intravenous injections, etc.). Age, hygiene habits, conditions of development (in or out of the hospital), and the nature of comorbidities can also affect the prevalence of certain causative agents in each case of IE (degree of the contamination of skin and mucous membranes, intestinal colonization), as well

as the immune response of macroorganism (DM, HIV infection in the absence of ART, chemotherapy for malignant neoplasms). However, despite the required clinical assessment of the characteristics of the alleged causative agent for empirical antibiotic therapy, one should aim for an accurate etiological diagnosis of IE by bacteriological and serological methods. A positive result of blood culture test is one of Duke's major diagnostic criteria that allows performing effective antibiotic treatment and predicting the course of the disease.

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ПРЕДИКТОРЫ СНИЖЕНИЯ МИНЕРАЛЬНОЙ ПЛОТНОСТИ КОСТНОЙ ТКАНИ У ПАЦИЕНТОВ С ЛИМФОМОЙ ХОДЖКИНА, АССОЦИИРОВАННЫЕ С ПАТОГЕНЕТИЧЕСКОЙ ТЕРАПИЕЙ

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Predictors of Bone Mineral Density Reduction in Patients with Hodgkin's Lymphoma Associated with Pathogenetic Therapy

Резюме

Лимфома Ходжкина чаще встречается в популяции молодых пациентов. Увеличение общей и безрецидивной выживаемости увеличивает вероятность развития постцитостатических осложнений в виде снижения минеральной плотности костной ткани и связанных с этим низкоэнергетических переломов. **Целью работы** является оценка факторов риска снижения минеральной плотности костной ткани у пациентов с лимфомой Ходжкина после стандартной полихимиотерапии и аутологичной трансплантации гемопоэтических стволовых клеток. **Материал и методы.** В исследование включены 118 человек, из них 88 человек — пациенты с лимфомой Ходжкина и 30 человек — группа контроля. Исследуемая группа пациентов с лимфомой Ходжкина разделена на 2 группы: пациенты, получившие стандартную полихимиотерапию, и пациенты, получившие стандартную полихимиотерапию и аутологичную трансплантацию гемопоэтических стволовых клеток. Для всех пациентов измерения минеральной плотности кости проводились с использованием сканера HologicDiscovery QDR (США) в поясничном отделе позвоночника (L2 — L4) и в области бедра (общая площадь бедра и шейки бедра). Были выбраны минимальные измерения минеральной плотности костной ткани и Т-критериев в области бедра и шейки бедра, для молодых пациентов подсчитан Z-критерий. **Результаты.** По результатам денситометрии в обеих исследуемых группах не наблюдалось снижение минеральной плотности костной ткани ниже возрастной нормы. У 13 пациентов (30 %), получивших аутологичную трансплантацию гемопоэтических стволовых клеток, выявлено снижение Т-критерия, что соответствует остеопении и остеопорозу. В группе стандартной ПХТ снижение Т-критерия наблюдается у 6 пациентов (14 %): до остепении — у 3 пациентов (7 %), до остеопороза — у 3 пациентов (7 %). Все пациенты с лимфомой Ходжкина, включенные в исследование, получали высокие дозы глюкокортикостероидов. Не выявлено зависимости снижения МПК, Z-критерия и риска низкоэнерге-

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тического перелома от стадии и варианта заболевания. **Заключение.** Высокая частота встречаемости снижения плотности костной ткани с учетом благоприятного прогноза для жизни пациентов с лимфомой Ходжкина указывает на необходимость разработки схем профилактики развития остеопороза и остеопении.

Ключевые слова: *Лимфома Ходжкина, денситометрия, остеопороз, минеральная плотность костной ткани*

Конфликт интересов

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

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Abstract

Hodgkin's lymphoma is more common in the younger patient population. An increase in overall and recurrence-free survival increases the likelihood of developing post-cytostatic complications in the form of a decrease in bone mineral density and associated low-energy fractures. **The aim of the work** is to evaluate risk factors for bone mineral density decrease in patients with Hodgkin's lymphoma after standard polychemotherapy and autologous hematopoietic stem cell transplantation. **Material and Methods:** The study included 118 people, of which 88 people were patients with Hodgkin's lymphoma and 30 people were the control group. The study group of patients with Hodgkin's lymphoma was divided into 2 groups: patients who received standard polychemotherapy and patients who received standard polychemotherapy and autologous hematopoietic stem cell transplantation. For all patients, measurements of bone mineral density were performed using the HologicDiscovery QDR scanner (USA) in the lumbar spine (L2–L4) and in the thigh region (total area of the thigh and femoral neck). The minimum measurements of bone mineral density and T-scores in the hip and femoral neck were selected, and the Z-score was calculated for young patients. **Results:** According to the results of densitometry in both study groups, there was no decrease in bone mineral density below the age norm. In 13 patients (30 %) who received autologous hematopoietic stem cell transplantation, a decrease in T-score was found, which corresponds to osteopenia and osteoporosis. In the standard PCT group, a decrease in the T-criterion was observed in 6 patients (14 %): to stagnation — in 3 patients (7 %), to osteoporosis — in 3 patients (7 %). All patients with Hodgkin's lymphoma included in the study received high doses of glucocorticosteroids. There was no correlation between the decrease in BMD, Z-criterion and the risk of low-energy fracture on the stage and variant of the disease. **Conclusion:** The high incidence of bone density reduction, taking into account a favorable prognosis for the life of patients with Hodgkin's lymphoma, indicates the need to develop schemes for the prevention of osteoporosis and osteopenia.

Key words: *Hodgkin's lymphoma, densitometry, osteoporosis, bone mineral density*

Conflict of interests

The authors declare no conflict of interests

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aHSCT — autologous hematopoietic stem cell transplantation, BMD — bone mineral density, CR — complete response, DXA — dual-energy x-ray absorptiometry, GCs — glucocorticosteroids, HL — Hodgkin lymphoma, PCT — polychemotherapy, PD — progression of disease, PR — partial response, SD — stabilization of disease

Introduction

Hodgkin lymphoma (HL) is a malignant disease of lymphatic system that develops in the impaired lymphopoiesis of B-lymphocytes in a lymph node and is characterized by typical lymphogenous metastasis [1]. This disease develops in people of any age group, with the peak incidence at the age of 20–35 years [2].

In recent years, the morbidity rate of HL has not changed significantly, however, the mortality rate has decreased along with the increased life expectancy of patients [3]. Survival prognosis for this disease is relatively favorable if advanced methods of treatment are used. Most patients can be cured after a standard first-line polychemotherapy (PCT) [2].

An advanced and very effective treatment method for relapsed or refractory HL is autologous hematopoietic stem cell transplantation (aHSCT) associated with the increased number of cured patients. However, the increased survival rate in HL is associated with increased possibility of complications (including

disabling and life-threatening) of previous cytostatic therapy. Many delayed complications of PCT and aHSCT include the pathological condition of musculoskeletal system that develops as a result of metabolic bone lesions — osteoporosis and the associated low-energy fractures [2, 3]. The mechanisms of osteoporosis development in patients with HL are poorly known. Several literature sources describe decreased bone mineral density (BMD) as a consequence of impaired formation and destruction of bone tissue, as well as increased bone resorption due to such factors as cytostatic agents, glucocorticosteroids (GCs), nutritional deficiency, sedentary lifestyle [3, 4]. In this context, the issues of diagnosis and preventing osteoporosis seem to be very relevant for oncohematology.

Objective of the study: to evaluate risk factors for BMD decrease in patients with Hodgkin lymphoma after standard PCT and aHSCT.

Materials and Methods

The retrospective study included 118 individuals, 30 of them were enrolled in the control group and 88 patients were admitted to the Department of Hematology, Chemotherapy and Bone Marrow Transplantation of the Sverdlovsk Regional Clinical Hospital No. 1 with confirmed HL.

The patients with proven diagnosis were divided into two study groups with equal number of participants (n = 44): group 1 — patients who received standard PCT (15 males (34 %), 29 females (66 %), median age 32.5 years), group 2 — patients who received standard PCT and aHSCT (22 males (50 %) and 22 females (50 %), median age 28 years). Group 3 — the control one — included 30 healthy volunteers (12 males (40 %), 18 females (60 %), median age 29 years). These groups were comparable in terms of demographic parameters and morphological characteristics of the disease.

Inclusion criteria were as follows: 1) reliable diagnosis of Hodgkin lymphoma; 2) indications for standard PCT and/or PCT + aHSCT. Exclusion criteria were as follows: 1) endocrine disorders (hypercorticism, thyrotoxicosis, etc.); 2) rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus); 3) gastrointestinal diseases (malabsorption syndrome, conditions after gastrointestinal surgery, liver failure); 4) history of cancer; 5) alcoholism and drug addiction.

HL was diagnosed based on the results of histological and immunohistochemical tests of biopsied lymph node.

This disease has two morphological forms: classical HL and nodular lymphocyte-predominant Hodgkin lymphoma that develops in only 5 % of total cases [1]. Classical HL, in turn, has 4 histological types with a common immunophenotype: nodular sclerosis (types I and II), mixed cellularity type, lymphocyte-rich classical type, and lymphocyte-depleted type [1]. The types with poor prognosis, i.e., lymphocyte-depleted and type II nodular sclerosis HL develop in no more than 10 % of cases [1, 2].

The patients in the groups were divided depending on the histological type of the disease. Most of them had nodular sclerosis — 40 patients (91 %) in group 1 and 41 patients (93 %) in group 2. There were only few patients with lymphocyte-depleted type — 1 patient (2 %) in group 2, as well as with mixed cellularity type — 4 patients (9 %) and 2 patients (5 %) in groups 1 and 2, respectively. Lymphocyte-rich classical type was not found (Table 1).

Depending on the stage of the disease, distribution in groups was as follows: group 1 — most patients had stage II of the disease; group 2 — most patients had stage III or IV. According to the results of the iliac bone trepanobiopsy in group 1, a tumor lesion of bone marrow

Table 1. *Characteristics in all study groups*

Categories	PCT Group (n=44)	The PCT+autoTGSK Group (n=44)	Control Group (n=30)
Stage			
I	0 (0.0 %)	0 (0.0 %)	–
II	22 (50.0 %)	13 (30.0 %)	
III	7 (16.0 %)	14 (32.0 %)	
IV	15 (34.0 %)	17 (39.0 %)	
A/B			
A	11 (25.0 %)	11 (25.0 %)	–
B	33 (75.0 %)	33 (75.0 %)	
Variant			
nodular sclerosis	40 (91.0 %)	41 (93.0 %)	–
mixed-cell	4 (9.0 %)	2 (5.0 %)	
lymphoid depletion	0 (0.0 %)	1 (2.0 %)	
Gender			
Female	22 (50 %)	29 (66 %)	18 (60 %)
Male	22 (50 %)	15 (34 %)	12 (40 %)

was found in 3 patients (7 %), in group 2 — in 12 patients (27 %).

The ratio of asymptomatic (A) and intoxication forms (B) in both groups was equal and amounted to: 11 individuals (25 %) with A form and 33 individuals (75 %) with B form, respectively. Thus, the predominance of B form in all groups was observed.

The most common first line therapy for patients with advanced HL is ABVD and enhanced BEACOPP regimen — escBEACOPP. Most patients in the aHSCT group received PCT according to BEACOPP regimen — 32 patients (73 %); according to ABVD regimen — 11 patients (25 %); according to COPDAC regimen — 1 patient (2 %). In the PCT group, most patients received treatment according to escBEACOPP regimen — 40 patients (91 %); 3 patients (7 %) — according to ABVD, besides, 1 patient (2 %) received therapy according to Gem-P regimen.

The number of courses was determined depending on the progression of the tumor process and the response to treatment. The average number of treatment courses was 4 (2 to 8). The average duration of PCT was (6 ± 2) months in aHSCT group and (8 ± 2) months in the PCT group. The patients did not receive radiation therapy for residual tumor.

As a result of the first line PCT, more than half of the patients in group 2 — 32 patients (73 %) — demonstrated partial response (PR). Eight patients (18 %) achieved stabilization of the disease (SD). The progression of the disease (PD) developed in 4 individuals in this group (9 %). In group 1, 33 patients (75 %) had complete response (CR) after the first line therapy; 11 patients (25 %) had PR.

After restaging, patients who had no CR received reserve therapy (2 to 7 courses), with the average number of 4 courses; in the PCT group, no reserve therapy was required.

The largest number of patients in group 2 received reserve therapy courses according to the following regimens: DHAP — 34 patients (77 %), escBEACOPP — 10 patients (23 %), DexaBEAM — 4 patients (9 %), Gemzar-including courses — 9 patients (20 %), HdCph, BEACOPP, BEACVPP — 1 patient each (2 %).

Generally, reserve therapy courses have improved treatment results: PR was achieved in 34 patients (77 %); it is 6 % higher compared to the first line of therapy. SD was established in 3 patients (7 %); it is 62 % less compared to the first line. CR was found in 6 patients (14 %); it is 67 % higher compared to the first line. PD was registered in only 1 patient (2 %); it is 75 % less than the previously obtained treatment result.

Currently, aHSCT is indicated as the standard of care for patients with relapsed or refractory HL. All patients of group 2 received this type of treatment. According to several researchers, aHSCT can increase long-term disease-free survival in HL patients from 30 to 65 %. According to our data, aHSCT was accompanied by CR in 29 patients (65 % of cases), and PR in 15 patients (35 % of cases).

All patients of study groups received no osteotropic therapy for osteoporosis as a preventive measures or regimen. Amount of treatment performed was determined in accordance with the response to the basic pathogenetic therapy. The patients received supportive treatment with proton pump inhibitors and diuretics.

The ongoing antineoplastic regimen therapy was associated with several side effects; among these, potential risk factors for decreasing BMD that increase the risk of fractures were analyzed. Development of changes in hormonal status after PCT and aHSCT was demonstrated, in particular, decreased androgenic function in men and decreased fertility in women [5]; there was also the onset of bowel diseases. Moreover, prolonged immobilization after aHSCT and weight loss are the risk factors for bone resorption disorders [3, 4].

Bone tissue disorder is assessed based on the measurement of BMD using dual-energy x-ray absorptiometry method (DXA). The assessment of densitometric parameters and bone tissue was carried out using dual-energy x-ray absorptiometry with HOLOGIC device (Hologic Inc, Bedford). Bone mass is calculated by the content of minerals per bone area unit (BMD, g/cm^2), a percentage of normal values in patients of the corresponding gender and age and peak bone mass [6]. At the same time, Z-score relative to age norm and T-score relative to peak bone mass were also calculated [6].

Values of DXA parameters depend on age, gender, and the onset of menopause. Normal T-score is considered to be ≥ −1.0; decreased BMD, or osteopenia, is T-score from −1.0 to −2.5; osteoporosis is characterized with T-score less than −2.5 standard deviations. In young individuals, normal Z-score is > −2.0; decreased BMD, or osteopenia, is Z-score ≤ −2.0. If young patients have a history of fractures of lower extremities, compression fractures of the spine, two or more fractures of the tubular bones of arms, as well as Z-score ≤ −2.0, it refers to a decrease in BMD and/or osteoporosis development [6].

T-score is recommended for the assessment of osteopenia and osteoporosis in 50+ patients [6], however, several sources admit using this parameter for this purpose in younger patients, if there are additional risk factors for decreased BMD [5, 7]. In patients with hemoblastosis who receive pathogenetic therapy, such factors include decreased androgenic and fertile function, long-term use of glucocorticoids, and cytostatic therapy [7]. In this regard, in the course of this study, T-score was used as an additional parameter characterizing the risk of decreased BMD.

During the study, a questionnaire survey of patients was conducted in order to identify risk factors, namely: previous fractures, hip fractures in parents, smoking, alcohol consumption, a history of diseases that contribute to the development of secondary osteoporosis (diabetes mellitus, hyperthyroidism, hypothyroidism, etc.).

In males 50+ and females in menopause, the signs of osteoporosis are more often found in the area of femoral neck, and in individuals younger than 50, in the area of lumbar spine [3, 8].

Data gathering, the subsequent correction, systematization of source information and visualization of the obtained results were carried out in Microsoft Office Excel (2016) spreadsheets. Statistical processing of the results was carried out using Python 3.8. Built-in functions from modules and Scipy were used for calculations. Quantitative parameters were assessed for compliance with normal distribution. To this end, the Shapiro — Wilk test was used. Samples of quantitative parameters with distribution other than normal were described using the values of median (Me) and the lower and upper quartiles (Q1–Q3) (Me [Q1; Q3]). The Mann — Whitney U test was used to compare independent samples. When comparing several samples of quantitative data with distribution other than normal, the Kruskal — Wallis test was used that is a non-parametric alternative variant to one-way analysis of variance. Nominal data were described with the indication of absolute values and percentages (%). The comparison of nominal data was carried out using the Pearson $\chi 2$ test. When the number of expected observations in any of the cells of the four-field table was less than 10, Fisher's exact test was used to assess the level of significance of the differences. We used the odds ratio (OR) and 95 % CI as a quantitative measure of effect when comparing relative parameters. In order to study the relationship between events represented by quantitative data with distribution other than normal one, a nonparametric method was used — the calculation of Spearman's rank correlation coefficient. The difference between parameters and identified relationships were considered statistically significant at $p \leq 0.05$.

The protocol was approved by the local ethics committee. Written informed consent was obtained from all patients prior to enrollment in the study.

Results

According to the results of densitometry, there was no decrease in BMD below the normal range in both study groups compared with the control group, as shown in Table 2.

In 11 patients (25 %) who received aHSCT, decreased T-score was found that corresponds to osteopenia (T-score in the range −1.0 to −2.5); in 2 patients (5 %) T-score was equal to −2.6 and −3, respectively. In the group of patients who received standard PCT, decreased T-score was found in 6 patients (14 %): in 3 patients (7 %) to osteopenia, and in 3 patients (7 %) to osteoporosis. BMD values in treatment groups demonstrated no statistically significant difference. In the control group, registered BMD, Z-score and T-score were within normal range.

The decrease in BMD in group 2 was 12 % higher than in the comparison group. At the same time, the degree of BMD decrease did not depend on the duration of the disease, the number of PCT courses, however, aHSCT caused significant decrease in BMD.

The relationship between BMI, the number of PCT courses, the dose of GCs, and the number of smoking patients is shown in Table 3.

When analyzing the prevalence of risk factors for decreased BMD, there were no significant differences in BMI and the number of smokers in studied groups (Table 3). Most patients in both groups were with overweight — 21 (48 %) and 24 patients (55 %), respectively. Body weight deficiency was found only in 2 patients (4.5 %) in group 1.

Due to certain differences in the dosing of GCs used to achieve remission in patients with HL, it seemed reasonable to analyze BMD values in groups that differed depending on the total dose of agents used in this group. Unfortunately, in the PCT group, such analysis turned out to be very difficult to perform due to the inclusion of a single case of a total dose of GCs less than 7,000 mg and the difficulty of its comparison with a subgroup of 43 individuals. However, in the group of HL patients who received aHSCT in addition to PCT, the detailing of this issue turned out to be quite consistent and demonstrated a definite aggravation of the decrease in BMD due to GCs in high doses when analyzing this parameter in any of the examined anatomical regions (Table 4).

The results of assessment the correlation of BMD in the examined area L1–L4 with disease stage are shown in Figure 1.

As one can see on Figure 1, no significant correlations could be identified between decreased BMD, Z-score, and the risk of low-energy fractures with the stage of the disease.

As known, the development of menopause is a significant risk factor for decreased BMD. The decrease in fertility in females and of androgenic function in males develops due to cytostatic agents. Alkylating agents (cyclophosphamide, procarbazine) in PCT regimens cause cytostatic damage to the ovaries in women and lead to a decrease in anti-Müllerian hormone level. PCT suppresses ovarian function and leads to secondary menopause [3, 5, 7].

Table 2. *Parameters of bone mineral density in the studied groups*

Parameters	PCT Group	The PCT+autoTGSK Group	Control Group	p
Number of patients	n=44	n=44	n=30	–
BMD (g/sm^2)	1.0 [0.97; 1.05]	0.93 [0.82; 1.03]	1.03 [0.0; 0.0]	–
Z-criterion	-0.4 [-2.8; 0.2]	-1.1 [0.5; -3.2]	-0.3[0.2; -1.9]	p2-1: < 0.001* p2-3: =0.0167* p1-3: =0.056
T-criterion L1-L4	-0.5 [-1.1; -0.2]	-1.27 [-0.4; -3]	0.0 [0.0; 0.0]	p2-1: =0.0235* p2-3: < 0.001* p1-3: =0.0128*
T-criterion hip neck	-0.5 [-1.1; -0.2]	-0.12 [-0.2; -2]	0.0 [0.0; 0.0]	p2-1: =0.025* p2-3: < 0.001* p1-3: =0.0486*
The T-criterion is general	-0.7 [-0.1; -1.2],	-0.39 [-0.1; -1.6]	0.0 [0.0; 0.0],	p2-1: =0.0018* p2-3: < 0.001* p1-3: =0.0414*

Note: p1-2 — reflects the differences between groups 1 and 2, p2-3 — reflects the differences between groups 2 and 3, p1-3 — reflects the differences between groups 1 and 3;
* statistically significant differences were noted at p <0.05

Table 3. *Risk factors for a decrease in BMD in the studied groups*

Factors	PCT Group (n=44)	The PCT+autoTGSK Group (n=44)	Control Group (n=30)	p
Body mass index, kg/m^2	25.28 [22.3; 28.35]	24.82 [22.78; 29.9]	23.71 [21.64; 25.35]	p2-1: =0.3567 p2-3: =0.0391 p1-3: =0.0770
Number of PCT courses	6±2	8±2	–	p1-2: < 0.001*
GCS: up to 7000 мг/mg more than 7000 мг/mg	 1 (2 %) 43 98 %)	 11 (25 %) 33 (75 %)	–	p1-2: =0.0058*
Smokers, people	16(36 %)	13 (30 %)	6 (20 %)	p2-3: =0.1825 p2-3: =0.2885 p1-3: =0.3109

Note: p1-2 — reflects differences between groups 1 and 2, p2-3 — reflects differences between groups 2 and 3, p1-3 — reflects differences between groups 1 and 3;
* statistically significant differences were noted at p <0.05

Table 4. *BMD values in groups of patients with LH in accordance with the total dose of GCS used*

Evaluation Area	Parameter	PCT Group			The PCT+autoTGSK Group		
		Up to 7000мг /mg GCS	More than 7000мг/mg GCS	p	Up to 7000мг /mg GCS	More than 7000мг/mg GCS	p
The number of patients depending on the received dose of GCS		n=1	n=43	–	n=11	n=33	–
Hip neck	**BMD (g/sm^2)**	0.81 [0.81;0.81]	0.82 [0.8;0.94]	0.3182	0.81 [0.76;0.88]	0.72 [0.64;0.78]	0.0122*
General	**BMD (g/sm^2)**	0.91 [0.91;0.91]	0.95 [0.88;0.99]	0.3762	0.91 [0.89; 0.99]	0.86 [0.71;0.91]	0.0167*
L1-L4	**BMD (g/sm^2)**	0.99 [0.99;0.99]	1.0 [0.97; 1.05]	0.4686	0.98 [0.91; 1.07]	0.91 [0.82;1.02]	0.0307*

Note: p1-2 — reflects the differences between groups 1 and 2, p3-4 — reflects the differences between groups 3 and 4; * statistically significant differences were noted at p <0.05

In this connection, we assessed bone density in postmenopausal women (with the absence of menstruation for more than 6 months) in studied groups, as shown in Table 5.

As one can see in Table 5, postmenopausal women in the aHSCT group had a decrease in BMD compared with the standard PCT group. No decrease in Z-score was found in the female patients of the studied groups. T-score levels in the female patients of the studied groups revealed no significant difference. There were no significant differences in the densitometric parameters of lumbar spine area in the groups of menopausal female patients.

The prevalence of osteopenia/osteoporosis based on BMD value in menopausal and non-menopausal women in the studied groups is shown in Figure 2.

As follows from the Figure 2, non-menopausal women in the studied groups more often demonstrated BMD levels within normal range; a decrease in this parameter to the level of osteopenia and osteoporosis was less often. These differences were revealed both in the PCT group and in the aHSCT group.

In the total cohort of enrolled patients, in the standard PCT group, fractures were registered in 11 patients (25 %); 3 of them (7 %) had the fractures of forearm, 8 patients (18 %) had the fractures of radius and ankle

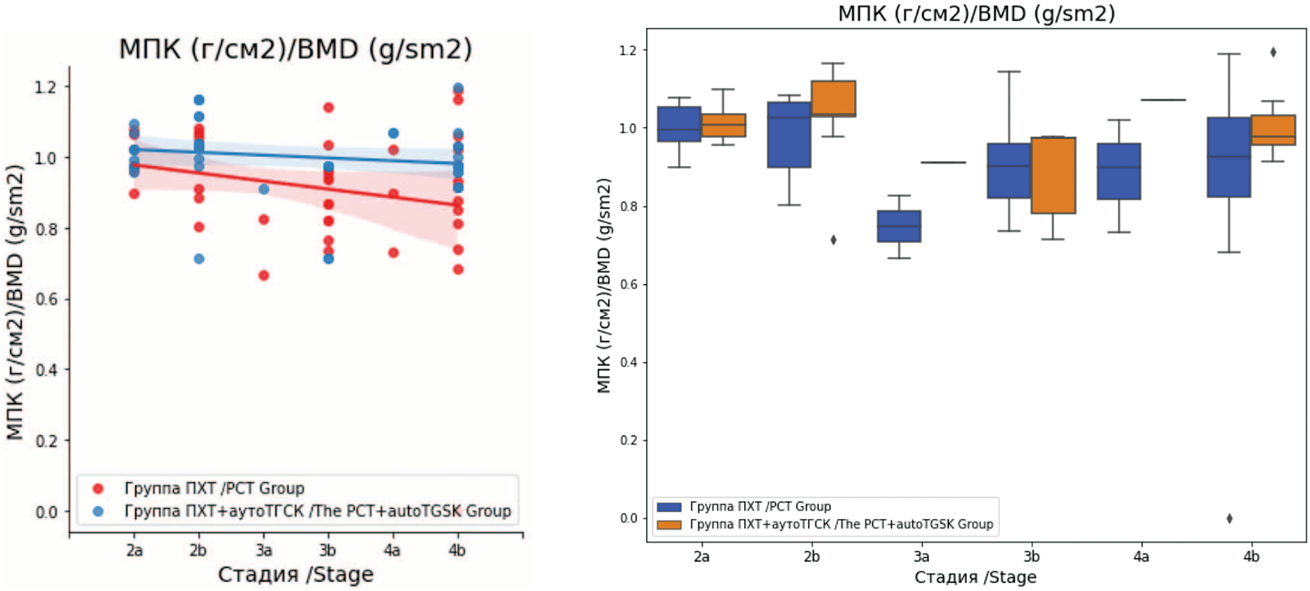

Figure 1. *Correlation between bone mineral density in the studied region of the lumbar spine (L1-L4) and the stage of the disease*

Table 5. *Characteristics of BMD in postmenopausal women in the study groups*

Evaluation Area	Parameter	PCT Group (n=11)	The PCT+autoTGSK Group (n=19)	p
Hip neck	BMD (g/sm²)	0.82 [0.72; 0.88]	0.7 [0.65; 0.78]	0.0509
	T-criterion	0.0 [-1.15; 0.0]	-0.8 [-0.8; -0.8]	0.2755
	Z-criterion	-0.1 [-1.35; 0.35]	-1.2 [-1.7; -0.5]	0.0273*
General	BMD (g/sm²)	0.98 [0.79; 1.04]	0.85 [0.73; 0.91]	0.0194*
	T-criterion	0.0 [-0.84; 0.4]	-0.2 [-0.2; -0.2]	0.2787
	Z-criterion	0.3 [-1.45; 0.7]	-0.7 [-1.6; -0.25]	0.0262*
L1-L4	BMD (g/sm²)	0.97 [0.81; 0.99]	0.9 [0.75; 1.0]	0.2066
	T-criterion	-0.4 [-2.1; 0.0]	-1.0 [-1.0; -1.0]	0.500
	Z-criterion	-0.8 [-1.95; -0.25]	-1.2 [-2.35; -0.15]	0.2518

Note: p1-2 — reflects the differences between groups 1 and 2; * statistically significant differences were noted at p ≤0.05

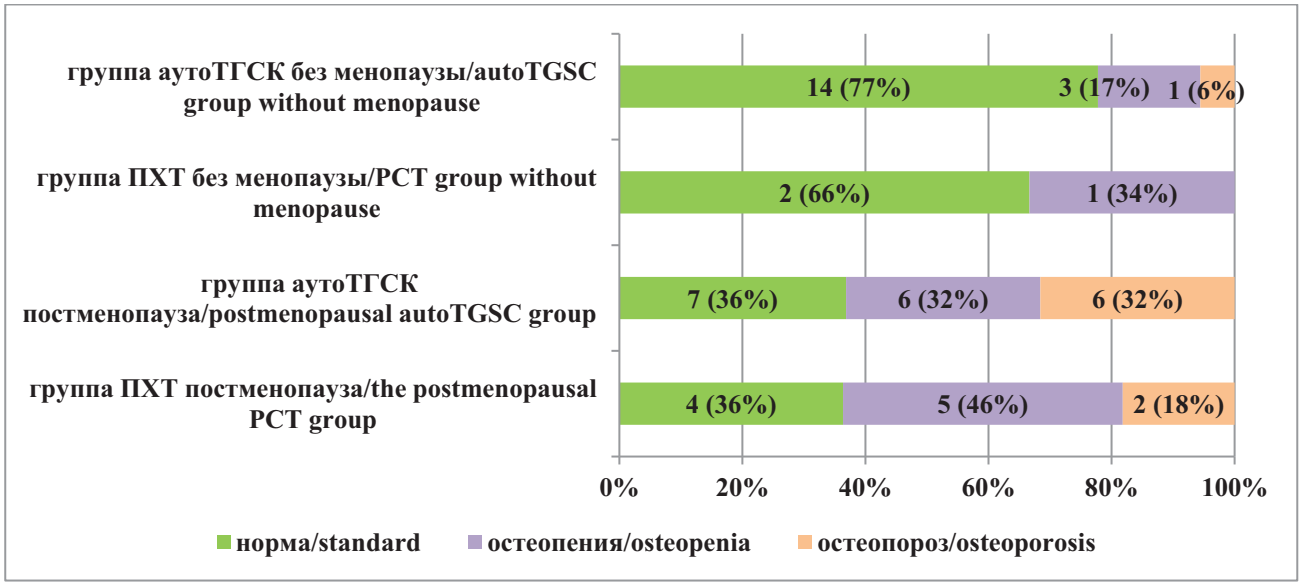

Figure 2. *The prevalence of osteopenia/osteoporosis based on bone mineral density in the study groups of patients without menopause and with menopause*

Note: all differences in the frequency of cases of osteopenia, osteoporosis and the registration of normal values in subgroups of patients with and without advanced menopause are significant at $p < 0.05$ in the groups of PCT and autoTGSK

joint bones. Eleven patients (25 %) in the aHSCT group had the fractures of radius, humerus, and ankle joint bones, and one patient (2 %) had the fractures of forearm bones. X-ray of the spine in lateral view revealed no evidence of compression fractures of vertebrae. All fractures in patients of both groups took place in childhood and adolescence as a result of traumatic injury.

According to the results of the X-ray of bones, avascular necrosis of femoral head was found in 2 patients (4 %) in the standard PCT group and in 3 patients (7 %) in the aHSCT group. Areas of avascular necrosis were in the stabilization phase and required no surgical treatment; patients received non-surgical therapy. Due to the relatively small sample of patients and the fact that this complication was uncommon for the patients in both study groups, it was not possible to analyze the risk of its development in connection with the ongoing pathogenetic therapy.

According to the questionnaire completed by the patients of both groups, only 6 patients (7 %) had no risk factors, 10 patients (11 %) had one risk factor, 28 patients (32 %) had 2 risk factors, and 44 patients (50 %) had three or more risk factors.

Discussion

Questions of the pathogenetic relationship between HL and decreased BMD remain undetermined to a large extent. The clinical relevance of the disease in increasing the risk of osteoporosis and associated fractures appears to be controversial. Pathogenetic therapy is potentially of first importance in this respect.

The regimen management of HL has made it possible to achieve success in the form of more than 90 % cure rate [2, 3]. However, with the reference to improved results of disease management, physicians face the question of ensuring the adequate quality of life for patients, as well as preventing delayed complications of therapy, including osteoporotic changes in bone tissue. In this regard, the issue of routine diagnosis of the state of bone tissue after PCT remains unresolved.

According to the results of the study performed by M. Voitko et al. (2019), PCT and glucocorticoids in high doses lead to a negative effect on bone remodeling in half of patients with HL that is present in impaired collagen renewal in bones and elimination of microcracks, as well as in decreased mechanical properties of collagen and bone tissue [3, 9].

Osteopenia and osteoporosis as the complications of therapy for lymphoproliferative diseases are more common in HL patients [3]. Bone tissue disorders associated with pathogenetic therapy in this category of patients are clinically significant complications [3, 5, 9].

According to different literature sources, bone tissue acquisition takes place at the age of 20–30 years, therefore, patients in this age group are more susceptible to the development of osteopenia and osteoporosis due to ongoing cytostatic and GCs therapy [5, 9, 10].

Delayed effect after polychemotherapy (PCT) remain a considerable problem at the present time. HL develops

predominantly at the age of 16–35 years, that is, during peak bone acquisition. At the same time, impaired development of collagen cartilage of the bone matrix, impaired process of bone renewal, and angiopathy of periosteal vessels after PCT result in impaired quality parameters of bones [11, 12]. The use of cytostatic agents, glucocorticoids, as well as disease onset in the young age are probably the critical factors in osteoporosis development in this group of patients [2, 5, 10].

Main risk factors for a decrease in BMD after standard PCT and aHSCT include high-dose PCT, GCs, prolonged immobilization, low body mass index, nutritional deficiency [3, 5, 10]. The main evidence of the pathogenetic significance of these factors in the development of decreased BMD was demonstrated in the model of primary postmenopausal osteoporosis. This research generally confirms the role of pathogenetic therapy as a risk factor for osteoporotic fractures in HL patients who receive pathogenetic therapy.

At the same time, the most important risk factor for low-energy fractures in bone tissue disorders in HL patients is long-term use of GCs [2, 3, 5]. High doses of corticosteroids used in PCT regimens exacerbate the processes between bone formation and resorption, thus increasing the risk of developing bone tissue disorders. GCs, on the one hand, cause a slowdown in bone formation due to the later maturation of osteoblasts and inhibition of the activity of prostaglandins in relation to growth factors and mature osteoblasts, and on the other hand, they increase bone resorption due to decreased levels of calcitonin and calcium [6].

For patients who frequently receive GCs in high doses, repeated courses of GCs therapy have a negative effect on bone tissue increasing the risk of fractures by 20 % [3, 5, 9]. Modern regimens of PCT and HSCT increase the risk of a decrease in BMD by several times [3].

According to Kanis et al. (2004), previous fractures increase the risk of subsequent fractures with the same frequency in men and women [11]. There is evidence that a fracture in a common location (proximal femur, spine, humerus) significantly increases the risk of subsequent fractures [11]. In the studied groups of patients, previous fractures in individuals who received standard PCT and aHSCT in addition to PCT were found in an equal number of patients (11 individuals, 25 %). All fractures in patients of the studied groups were the result of traumatic injuries in childhood and adolescence.

The decrease in bone density was more pronounced in the aHSCT group than in the standard PCT group indicating a corresponding increase in the risk of osteoporosis. A similar pattern is observed when analyzing the risks of decreased BMD in postmenopausal women [10]. In postmenopausal women on aHSCT, there is a decrease in BMD that is not observed in the standard PCT group. At the same time, it is important to emphasize that, in general, HL patients at different stages of treatment require the analysis of bone tissue during the early period after therapy in order to assess the risk of decreased BMD and timely start the prevention and management of osteoporosis.

Conclusion

HL patients who receive PCT with GCs are at the high risk of osteopenia and osteoporosis. Such known factors as the stage and type of the disease have no effect on the decrease in BMD in HL patients. However, aHSCT significantly increases the risk of BMD decrease. Considering a favorable prognosis, the high incidence of decreased bone density requires the development of osteoporosis- and osteopenia-preventing regimen for this category of patients.

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ДИНАМИКА ВОССТАНОВЛЕНИЯ ПАЦИЕНТОВ С ИШЕМИЧЕСКИМ ИНСУЛЬТОМ В ЗАВИСИМОСТИ ОТ ПОКАЗАТЕЛЕЙ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ И ЕГО ВАРИАБЕЛЬНОСТИ

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Recovery Dynamics in Patients with Ischemic Stroke Depending on the Blood Pressure Indicators and Its Variability

Резюме

Цель — изучение неврологического и функционального восстановления у пациентов после ишемического инсульта в зависимости от показателей артериального давления (АД) и его вариабельности. **Материалы и методы**: обследовано 150 пациентов с ишемическим инсультом и артериальной гипертонией (АГ), которые находились на стационарном лечении в неврологическом отделении (76 (50,7 %) мужчин и 74 (49,3 %) женщин, средний возраст 67,4±7,3 лет). Всем пациентам проводили общепринятые физикальные и лабораторные исследования, измерение АД в динамике; для оценки тяжести неврологического дефицита на момент поступления в стационар, в динамике острого периода (до 21 суток) и на 21 сутки использовалась Шкала тяжести инсульта Национальных институтов здоровья США — NIHSS (National Institutes of Health Stroke Scale). **Результаты.** Установлено, что последствия острого периода инсульта зависят от уровня АД и его вариабельности в начале острого периода. Более чем 50–процентная вероятность снижения балла по NIHSS наполовину (от исходного) прогнозируется при наличии у пациента показателя стандартного отклонения (SD) систолического артериального давления (САД) на 1– 3 сутки менее 12,4 мм рт. ст. Кроме этого, SD САД на 1– 3 сутки и 1– 6 сутки, и SD диастолического артериального давления (ДАД) с 1 по 3 сутки являются наиболее значимыми при оценке связи со степенью функциональных нарушений в конце острого периода инсульта. **Заключение.** Уровень АД и его вариабельность в течение острого периода ишемического инсульта позволяют прогнозировать тяжесть неврологического дефицита и функциональные последствия инсульта в восстановительном периоде (до 21 суток).

Ключевые слова: *ишемический инсульт, артериальная гипертония, функциональный дефект, функциональное восстановление, вариабельность артериального давления*

Конфликт интересов

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

Источники финансирования

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Abstract

The study aims to neurological and functional recovery in patients after ischemic stroke depending on blood pressure (BP) parameters and its variability. **Materials and methods**: We examined 150 patients with ischemic stroke and arterial hypertension (AH) who were hospitalized in the neurological department (76 (50,7 %) men and 74 (49,3 %) women, mean age 67,4±7,3 years). All patients underwent standard physical and laboratory examinations, measurement of blood pressure in dynamics; The National Institutes of Health Stroke Scale (NIHSS) was used to assess the severity of neurological deficits at the time of admission to the hospital, in the dynamics of the acute period (up to 21 days) and on the 21st day. **Results:** It was found that the consequences of the acute period of stroke depend on the level of blood pressure and its variability at the beginning of the acute period. A more than 50 percent probability of a decrease in the NIHSS score by half (from baseline) is predicted if the patient has a standard deviation (SD) systolic blood pressure (SBP) less than 12,4 mm Hg on days 1– 3. In addition, SD SBP on days 1– 3 and 1– 6 days, and SD diastolic blood pressure (DBP) from 1 to 3 days are the most significant in assessing the relationship with the degree of functional impairment at the end of the acute period of stroke. **Conclusion:** The level of blood pressure and its variability during the acute period of ischemic stroke makes it possible to predict the severity of the neurological deficit and the functional consequences of stroke in the recovery period (up to 21 days).

Key words: *ischemic stroke, arterial hypertension, functional defect, functional recovery, blood pressure variability*

Conflict of interests

The authors declare no conflict of interests

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ADMV — average of daily mean value, AH — arterial hypertension, BI — Barthel index, BP — blood pressure, CT — computed tomography, DBP — diastolic blood pressure, ECG — electrocardiography, IS — ischemic stroke, MRI — magnetic resonance imaging, NIHSS — National Institutes of Health Stroke Scale, ROC — receiver operating characteristic, SBP — systolic blood pressure, SD — standard deviation, TCD — transcranial Doppler

Introduction

Severe social consequences of stroke and high costs of its management encourage the medical community to improve the measures for prevention and treatment of acute cerebrovascular accident [1, 2], rehabilitation approaches [3–5], and predicting the consequences of an acute cerebral accident [6–8]. High systolic blood pressure (SBP) is one of the main modified risk factors for stroke that determine its severity [9–11]. The problem of stroke with underlying arterial hypertension (AH) is very urgent in Russia, given the fact that according to the Ministry of Health of the Russian Federation, 4,303 thousand patients with cardiovascular diseases were registered in 2020 compared to 2000 when this value was 2,483 thousand of the entire population (according to the information of Federal State Statistics Service for 2020, https://rosstat.gov.ru/folder/13721).

Much attention is paid to the analysis of blood pressure (BP) levels and the parameters of neurological recovery after ischemic stroke (IS) [12–15]. It is thought that BP variability can be a predictor of IS consequences [16, 17], however, its correlation with the stroke characteristics in the acute period, the timing of BP measurement, and stroke outcome remains debatable [18, 19].

Hypertension is a key risk factor for vascular cognitive disorders, in particular, stroke [20], and stroke is one of the determining factors in the progression of vascular dementia [21–23]; its prevalence after the first IS increases to 23 % [24]. Meanwhile, the changes of functional disorders over time in the post-stroke period that depend on the stage of AH, indicators of cerebral atherosclerosis, BP variability, especially at the disease onset, remain unknown.

The **objective** of the study was to analyze the neurological and functional rehabilitation of patients after ischemic stroke depending on BP parameters and variability.

Materials and Methods

This study is based on the analysis of 24-hour BP variability and on the assessment of the severity of neurological deficit in 150 patients (76 (50.7 %) males and 74 (49.3 %) females, mean age (67.4 ± 7.3) years) with ischemic stroke and AH hospitalized into the Neurological Department of Borisov Central District Hospital at the period from 2018 to 2021. During this study,

the course of IS associated with underlying essential AH within six months from stroke was analyzed in details.

Inclusion criteria: primary ischemic stroke (ICD-10I code 63.5), signing the voluntary informed consent form, hospitalization within 6 hours after stroke, history of essential (primary) hypertension, possibility of contact with the patient and their family during the entire follow-up period, obtaining information from medical records, interviews or emails.

Exclusion criteria: hemorrhagic stroke, recurrent ischemic stroke, ischemic stroke of unknown subtype, secondary (symptomatic) hypertension, coma.

Before the start of the examination of patients, informed consent was obtained for their participation in this study in accordance with the standards of the Declaration of Helsinki of the World Medical Association Ethical Principles for Conducting Medical Research Involving a Person as a Subject and the Rules of Clinical Practice in the Russian Federation approved by the Order of the Ministry of Health of the Russian Federation No. 266 dated June 19, 2003. Preliminary approval was obtained from the Committee on Bioethical Expertise and Research Ethics of the Medical Institute of the BelSU National Research University, record No. 56 dated February 12, 2019. In case of pronounced neurological deficit (paresis or plegia of upper limbs, impaired higher cortical functions, etc.), the informed consent was signed by patient's legal representatives — relatives or other legally authorized persons.

The patients were monitored during the admission and hospital stay, in the acute period of stroke on day 21 and within six months from the IS onset. Endpoints: BP level, severity of neurological deficit, Barthel index.

The ischemic stroke was diagnosed based on the results of clinical and neurological examination and confirmed by the results of a neuroimaging examination of brain according to the protocol for the management of patients with stroke of the National Standard of the Russian Federation, 2009 [25] and the Guidelines (Procedures) for the Provision of Emergency Medical Care in Acute Cerebrovascular Events [26].

AH was diagnosed according to the National Clinical Guidelines on Hypertension in Adults (2020) [27]. BP was registered using one standardized mechanical blood pressure monitor Gamma 700K. BP was measured according to the standard method in relaxed environment after a 5-minute rest [27]. BP was measured during hospitalization: repeated measurements were taken every 4 hours for 6 days after IS onset. BP variability was assessed using the following parameters: mean SBP, DBP, maximum SBP and DBP values, standard deviation (SD) estimated for SBP and DBP at each timepoint within 6 days and for the intervals of day 1–3, day 1–6, day 3–6.

On discharge from the hospital, each patient and their relatives were provided with detailed oral and written instructions on correct measuring blood pressure at home; their ability to master this skill was checked; it was suggested to keep a BP monitoring log as per the developed guidelines for BP measuring at home [27]. The patients were recommended to measure BP twice a day: in the morning (before taking medications) and in the evening (before meals). At the end of each month within six months after discharge from the hospital, information on the measured BP values was collected by phone.

To assess the severity of neurological deficit on admission and over time on day 21, the authors used the US National Institutes of Health Stroke Scale (NIHSS) — a validated and commonly used method for the standardized assessment of stroke severity [28–30].

To monitor functional recovery in the acute period and within six months after IS, Barthel index (BI) that assesses the activities of the daily living of patients was used [31, 32].

During their hospital stay, the patients received antihypertensive therapy prescribed after the consultation with a cardiologist in accordance with the corresponding domestic guidelines [27]. After discharge from the hospital, the recommended antihypertensive therapy continued under the supervision of a family physician.

All patients underwent standard laboratory tests and instrumental examinations that included standard 12-lead ECG, brain magnetic resonance imaging (MRI), ultrasound duplex of the vessels of head and neck, and transcranial Doppler (TCD).

Almost half of the examined patients (48.0 %) had cortical and subcortical lesions of brain, see Table 1.

In should be noted that 22 (14.7 %) patients had one lesion and 128 (85.3 %) patients had two lesions. Small (up to 15 mm in diameter), medium (15–30 mm) and large (more than 30 mm) lesions were diagnosed with the same statistical frequency, see Table 2.

Table 1. *Localization of the focus of ischemia in patients with hypertension*

Localization	Abs.	%
Cortical-subcortical	72	48,0
Subcortical	23	15,3
Basal ganglia	29	19,3
Stem-cerebellar	26	17,3

Table 2. *The size of the focus of ischemic stroke*

Size, mm	Abs.	%
More than 30	51	34,0
15-30	59	39,3
Under 15	40	26,7

Stage 1 AH was observed in 30 (20 %) patients, stage 2 AH — in 72 (48.0 %) patients, stage 3 AH — in 48 (32 %) patients, see Figure 1.

The patients were divided into groups according to AH duration: with the onset up to 5 years ago, 6 to 10 years ago and more than 10 years ago. 28 (18.7 %) patients reported of the duration of the disease up to 5 years, 67 (44.7 %) — 6 to 10 years, 55 (36.7 %) — more than 10 years.

Alongside with AH, the examined patients had other comorbidities. Coronary heart disease was found in 137 (91.33 %) patients, including CHD with atrial fibrillation — in 22 (14.67 %), type II diabetes mellitus — in 17 (11.33 %), past myocardial infarction — in 13 (8.67 %) patients, chronic diseases of gastrointestinal tract — in 97 (64.67 %), of lungs — in 37 (24.67 %), of kidneys — in 7 (4.67 %) patients.

On admission, the severity of neurological deficit according to the NIHSS scale ranged from 3 to 20 points, with average value of 12.5 (6.3–18.6) points. The distribution of patients with ischemic stroke according to NIHSS score is shown in Figure 2.

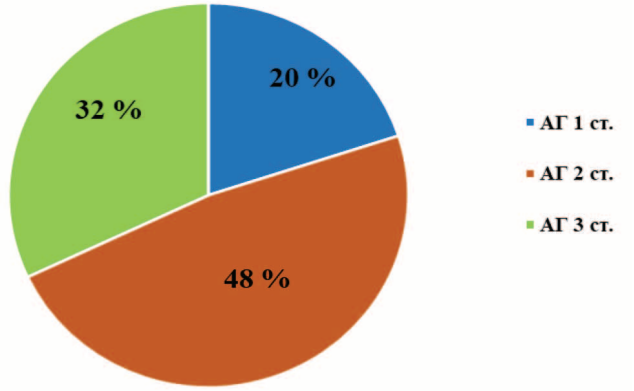

Figure 1. *Distribution of patients according to the degree of arterial hypertension, %*

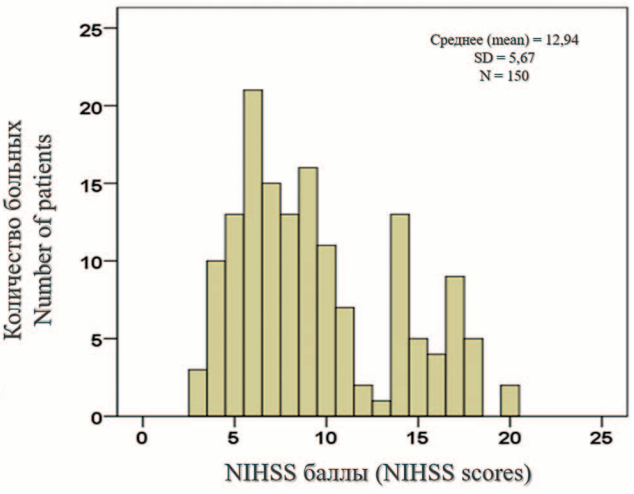

Figure 2. *Distribution of patients with ischemic stroke by NIHSS score*

Statistical processing of the obtained results was performed using IBM SPSS Statistics Base v.22 software for statistical analysis. Data for parameters with normal distribution are presented as arithmetic mean and standard deviation (M ± SD), and for parameters with non-normal distribution — as a median with interquartile range (Me (IQR)). Parametric methods were used for quantitative parameters with normal distribution; in other cases non-parametric methods were used. To assess qualitative parameters, parameters with non-normal distribution, and parameters with indeterminate distribution, Spearman's correlation coefficient was used. Pearson correlation coefficient was used to measure the degree of linear relationship between two variables in assessing quantitative parameters. For comparative analysis of samples with normal distribution, ANOVA analysis of variance and paired Student's t-test for independent and dependent samples were used. To compare three or more separate groups, the Kruskal — Wallis test and the median test were used. Independence test was performed using the chi-square test with Yates's correction for continuity and Fisher's exact test. For analysis of samples that did not correspond to the laws of normal distribution, the following non-parametric methods were used: paired Wilcoxon test for related samples and Mann — Whitney U test for independent samples.

The changes in the recovery of neurological deficit over time (decrease in NIHSS score in %) were calculated using the formula [29]:

$$\frac{100 \times (\text{NIHSS score on day 1} - \text{NIHSS score on day 21})}{\text{NIHSS score on day 1}}$$

To analyze BP variability in this study, we used standard deviation (SD). To assess the role of SBP SD parameters on days 1–3 as a predictor of stroke severity according to NIHSS at discharge, we used binary logistic regression analysis with the coefficient of determination (R^2).

Results and Discussion

During hospitalization in the Emergency Department, mean SBP was (163.17 ± 2.04) mm Hg, although according to the documents of emergency team, this parameter by the time of the first measurement after stroke development was significantly higher (p = 0.001) and amounted to (181.13 ± 2.02) mm Hg. This was probably the result of the use of medications at the prehospital stage.

After 8 hours, mean SBP was significantly higher than on admission: (177.8 ± 2.4) mm Hg, (p = 0.001). Subsequently, during the next 56 hours, there was a trend towards a decrease in mean BP and its stabilization at

the level that was before stroke. Mean DBP values were characterized by the absence of significant fluctuations during the first 12 hours and by a smaller range of these fluctuations. At the same time, one should mention that in the acute period (first two days) a large range of individual daily fluctuations in the values of systolic and diastolic pressure remained: from 280 to 100 mm Hg and from 100 to 60 mm Hg, respectively (statistically significant differences on day 1 and day 2 compared to other days, $p < 0.05$), see Figure 3.

One of the objectives of this study was to determine the parameters that characterize AH course and are associated with the severity of neurological deficit in the presence of stroke on admission.

In strokes with neurological deficits of different severity, mean SBP values significantly differed at 8, 12, 16, and 20 hours. After 24 and 28 hours, significant differences remained only between mild and severe stroke in terms of mean systolic blood pressure values, see Table 3.

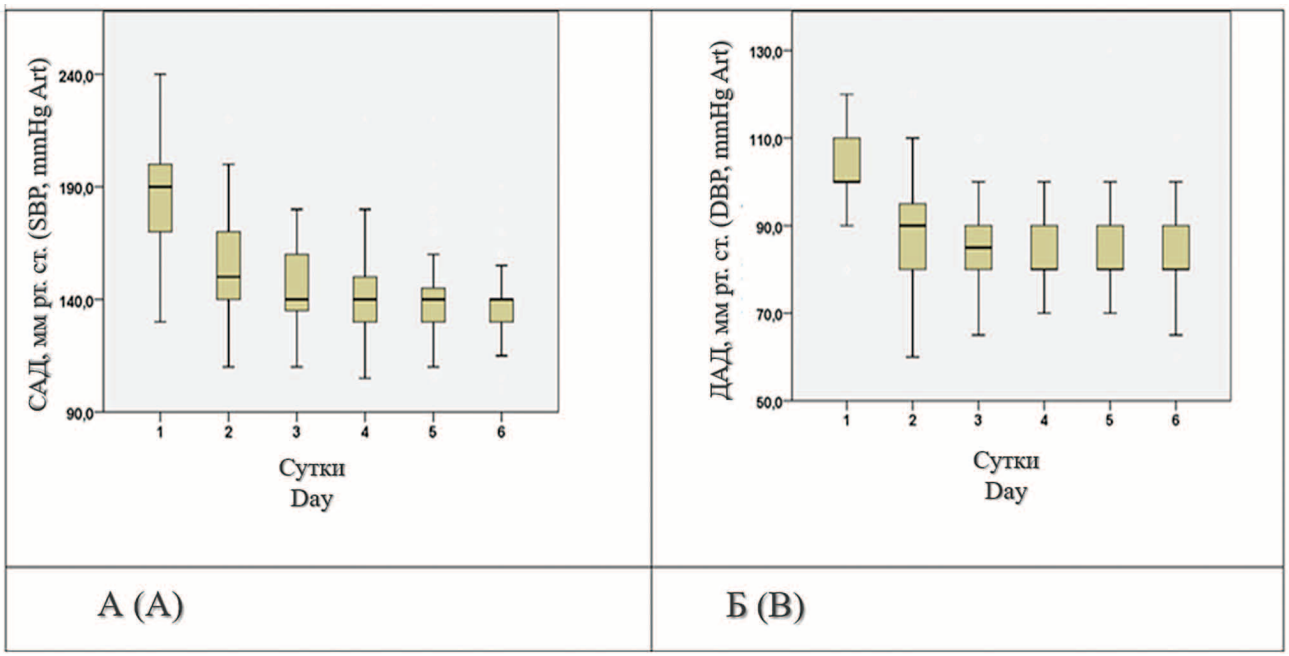

Figure 3. *Medians and quartiles of SBP (A) and DBP (B) values for the first six days of the acute period of stroke*
Note: SBP — systolic blood pressure, DBP — diastolic blood pressure (Days 1 and 2, SBP and DBP significantly differed from BP values on the following days, $p < 0.05$)

Table 3. *Mean SBP values in the first two days of stroke depending on the severity of neurological deficit according to NIHSS upon admission to the hospital (M±SD)*

Time after stroke, hour	The severity of the neurological deficit			p– value		
	Легкая/ Mild n=26	Средняя/ Medium n=86	Тяжелая/ Severe n=38	1vs 2	1 vs 3	2 vs 3
4	160,9±17,3	166,2±26,0	157,6±25,3	0,525	0,895	0,265
8	157,1±22,9	173,0±25,0	202,6±25,3	**0,003**	**0,001**	**0,001**
12	150,8±21,4	163,7±23,2	184,4±26,5	**0,012**	**0,001**	**0,001**
16	148,1±17,3	157,2±21,3	170,1±25,9	**0,035**	**0,001**	**0,007**
20	142,9±14,3	152,6±19,5	162,5±25,3	**0,021**	**0,001**	**0,006**
24	141,4±10,7	148,4±19,5	156,7±25,9	0,095	**0,006**	0,097
28	139,4±13,8	145,6±18,5	155,7±24,0	0,088	**0,005**	**0,036**
32	137,7±15,8	146,5±17,4	145,6±25,3	**0,035**	0,065	0,996
36	141,9±20,4	144,4±16,7	146,7±25,3	0,467	0,258	0,462
40	138,6±16,8	142,7±16,3	139,2±20,9	0,181	0,792	0,178
44	137,7±13,8	139,7±13,9	137,2±19,1	0,718	0,879	0,547
48	136,7±14,3	137,9±13,0	136,3±20,9	0,682	0,923	0,584

Note: p– values — significant differences between respective groups, SBP — systolic blood pressure

Mean DBP values (mm Hg) turned out to be less sensitive in indicating differences between different stroke severity and reliably demonstrated the difference between three stages only after 8 hours ((98.3 ± 12.2) mm Hg — mild neurological deficit, (101.3 ± 25.0) mm Hg — moderate, and (112.5 ± 28.7) mm Hg — severe neurological deficit, all p values < 0.05) and partly after 12 hours (significant difference was only between mild ((99.8 ± 16.3) mm Hg) and severe ((115.2 ± 22.2) mm Hg) stages of neurological deficit, p = 0.001) after acute cerebrovascular accident.

Considering the fact that in the acute period of stroke a significant range of individual 24-hour BP fluctuations is registered, a possible informative indicator of the progress of stroke (a prognostic factor) may be the 24-hour BP variability, calculated as a standard deviation from 24-hour average BP.

Analysis of SBP variability during 24 hours in the most acute period of stroke revealed the highest mean SD value on day 1 that was (18.7 ± 4.4) mm Hg, with fluctuations in individual SD values from 10.3 to 23.2 mm Hg. Mean SBP SD for the first three days ((18.9 ± 3.5) mm Hg) was also significantly higher compared to the values for days 2–6 ((9.6 ± 2.3) mm Hg), p = 0.001.

Maximal spread of individual values of SBP SD during 24 hours was observed on day 1 (Me 17.7, the second quartile — 11.6, the third quartile — 24.2), as well as in the period from day 1 to day 4, as evidenced by median and interquartile range, see Figure 4.

Mean SBP SD for the first three days was also reliably higher (19.4 (IQR: 12.2–23.1) mm Hg compared with the values for days 2–6 (10.35 (IQR: 5.9–14.3) mm Hg), p = 0.001.

Patients with IS of different severity demonstrated significant differences in terms of SBP SD per 24h on day 1 (p = 0.010). On day 2, there were differed significant differences in this value between mild and severe IS and between moderate and severe CIS, see Table 4.

It was found that the average values of daily mean SBP values during 24 hours in the acute period correlate with the severity of stroke (in points) at the time of discharge. There were significant correlations for day 1 (r = 0.396, p = 0.001), day 2 (r = 0.265, p = 0.001), within days 1–3 (r = 0.303, p = 0.001), and within days 1–6 (r = 0.239, p = 0.003) (Table 5). In patients with moderate and severe stroke, correlation coefficients of the standard deviation for daily mean SBP with the stroke severity increased to 0.725 (p = 0.001) on days 1–3 and to 0.695 (p = 0.001) on days 1–6. On discharge, there was moderate correlation between maximum DBP and NIHSS score (r = 0.472, p = 0.001) only on day 1. According to the data for days 1–3 of follow-up, DBP SD and NIHSS score on discharge also demonstrated moderate correlation (r = 0.550, p = 0.001) (Table 5). The table demonstrates that SBP SD and DBP SD turned out to be more informative indicators for correlation between the indicators of AH progress in the acute period and the regression of neurological deficit.

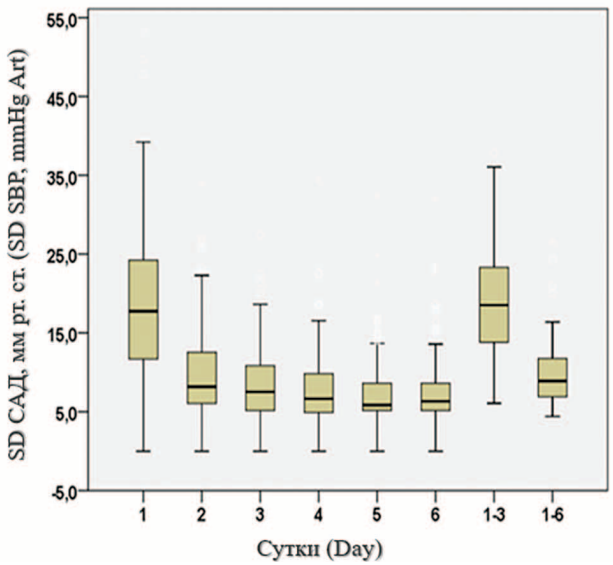

Figure 4. *Meaning of SD SBP medians and quartiles at different times from the onset of stroke*

Table 4. *Comparative assessment of SD SBP per day (Me(IQR)) depending on the severity of neurological deficit*

Time after stroke, day	The severity of the neurological deficit			p–value		
	Mild n=26	Medium n=86	Severe n=38	1vs 2	1 vs 3	2 vs 3
	SD	SD	SD	1/2	1/3	2/3
1	12,1(9,2-15,1)	18,6(15,8-21,4)	24,0(22,1-25,9)	**0,010**	**0,001**	**0,001**
2	7,3(6,4-8,2)	9,1(6,8-11,5)	12,1(8,9-15,1)	0,241	**0,015**	**0,014**
3	6,5(4,8-8,3)	7,3(6,2-8,5)	9,7(7,9-11,5)	0,338	0,040	0,059
4	5,5(3,6-7,4)	7,1(5,9-8,3)	8,0(5,9-10,2)	0,031	0,060	0,613
5	6,1(4,8-7,5)	7,0(5,4-8,6)	7,4(6,5-8,3)	0,145	0,902	0,108
6	7,5(4,7-10,3)	6,5(5,1-7,9)	8,3(6,9-9,8)	0,772	0,523	0,497
1-3	14,3(12,4-16,3)	18,2(16,5-19,9)	26,2(24,5-28,0)	**0,001**	**0,001**	**0,001**

Note: SBP — systolic blood pressure; SD — standard deviation; p– values — significant differences between respective groups

Table 5. Correlation Coefficients Between NIHSS Score at Discharge and BP Indicators

Parameter	r	p		Parameter	r	p
AVADV SBP, 1 day	0,396	0,001		SD SBP, 1 day	**0,487**	0,001
AVADV SBP, 1– 3 days	0,303	0,001		SD SBP, 2 day	0,244	0,003
AVADV SBP, 1– 6 days	0,239	0,003		SD SBP, 3 day	0,194	0,018
SBP max, 1 day	0,383	0,001		SD SBP, 1– 3 days	**0,725**	0,001
SBP max, 2 day	0,265	0,001		SD SBP, 1– 6 days	**0,695**	0,001
AVADV DBP, 1 day	0,337	0,001		SD DBP, 1 day	0,330	0,001
AVADV DBP, 6 day	0,182	0,026		SD DBP, 4 day	0,172	0,035
AVADV DBP, 1 — 3 days	0,162	0,048		SD DBP, 1 — 3 days	**0,550**	0,001
DBP max, 1 day	**0,472**	0,001		SD DBP, 1 — 6 days	0,474	0,001
DBP max, 6 day	0,180	0,027		Duration of hypertension	**0,538**	0,001
Degree of hypertension	**0,481**	0,001				

Note: AVADV — the average value of the average daily value; SBP — systolic blood pressure; DBP — diastolic blood pressure; AH — arterial hypertension; SD — standard deviation; p– values — significant differences between respective groups

Univariate regression analysis revealed a significant dependence of stroke severity according to NIHSS on discharge on SBP SD on days 1–3, $R^2 = 0.526$, see Figure 5.

According to logistic regression analysis, there is a dependence between the decrease in NIHSS score on discharge and SBP SD on days 1–3. The final model has sensitivity of 93.9 %, specificity of 86.5 %, and diagnostic accuracy of 90.1 %, with ROC area of 0.957 (95 % CI: 0.94–0.99), p = 0.003, see Figure 6.

It was established that more than a 50 % chance of reducing the NIHSS score by half (from baseline) is predicted if a patient had SBP SD on days 1–3 less than 12.4 mm Hg, see Figure 7.

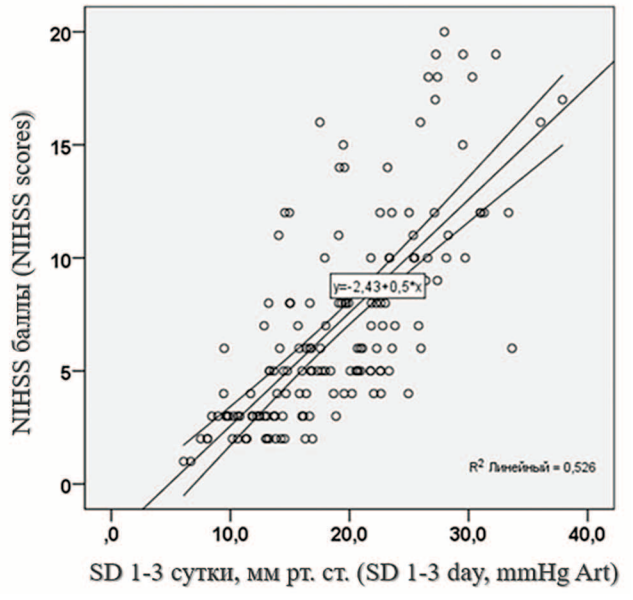

Figure 5. *Scatter diagram (with a line of approximation) of SD SBP on days 1– 3 depending on the severity of stroke according to NIHSS on day 21.*

Note: NIHSS — National Institutes of Health Stroke Scale; SD SBP — standard deviation of systolic blood pressure during the day

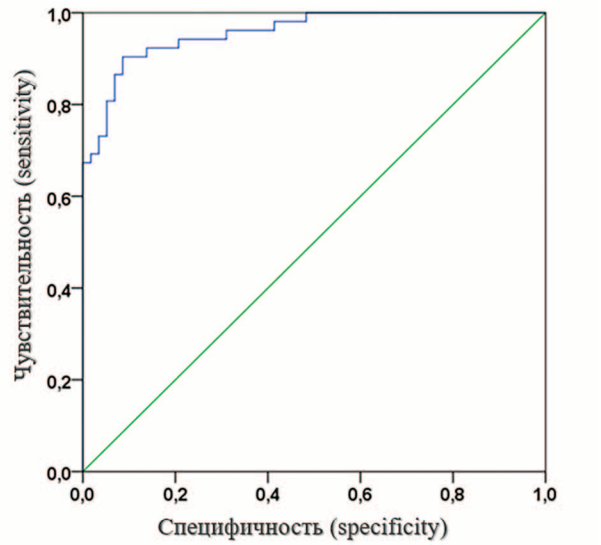

Figure 6. *ROC-curve of the prognostic model of Barthel index recovery one month after cerebral ischemic stroke*

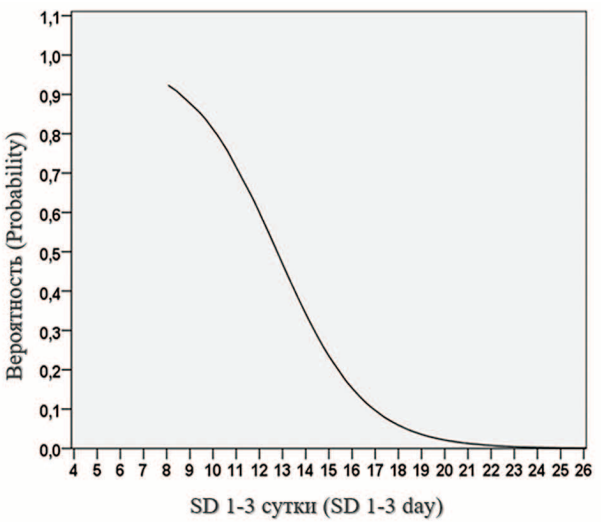

Figure 7. *Probability of NIHSS score decrease by 50 % (from baseline) depending on SBP SD value for 1– 3 days*

Note: SD — standard deviation of systolic blood pressure during the day

Table 6. *Correlation coefficients of the Bartel index for 21 days with blood pressure indicators*

Parameter	r	p		Parameter	r	p
AVADV SBP, 1 day	– 0,232	0,004		SD SBP, 1 day	**– 0,427****	0,001
AVADV SBP, 2 day	– 0,072	0,379		SD SBP, 2 day	– 0,199	0,015
AVADV SBP, 1– 3 days	– 0,147	0,072		SD SBP, 3 day	– 0,144	0,078
AVADV SBP, 1– 6 days	– 0,109	0,186		SD SBP, 1– 3 days	**– 0,551****	0,001
SBP max, 1 day	– 0,289	0,001		SD SBP, 1– 6 days	**– 0,515****	0,001
SBP max, 2 day	– 0,132	0,107		SD DBP, 1 day	– 0,233**	0,004
AVADV DBP, 1 day	– 0,223	0,06		SD DBP, 2 day	– 0,108	0,190
AVADV DBP, 2 day	– 0,31	0,703		SD DBP, 1– 3 days	**– 0,550**	0,001
DBP max, 1 day	– 0,349	0,001		SD DBP, 1– 6 days	– 0,317	0,001
DBP max, 2 day	– 0,018	0,825				

Note: AVADV — the average value of the average daily value; SBP — systolic blood pressure; DBP — diastolic blood pressure; SD — standard deviation; p– values — significant differences between respective groups

Thus, BP variability during the acute period made it possible not only to reveal differences between mean values in the case of cerebral ischemic strokes of different severity over time, but also to trace individual fluctuations in systolic and diastolic pressure in terms of the maximum severity of cerebral disorders, as well as to demonstrate the effect of daily variability, in particular, of SBP SD, on the consequences of stroke with defining the most informative corresponding terms.

At the end of the acute period on day 21, mean Barthel score was 68.3 (53.2–83.4) (from 0 to 95). The relationship between the grade of functional recovery in the acute period and BP parameters was analyzed (Table 6), namely: average values of daily mean SBP and DBP, maximum SBP and DBP, BP variability.

Correlation coefficients between SBP SD and Barthel index on day 1, days 1–3 and days 1–6 were r = –0.427 (p = 0.001), r = –0.551 (p = 0.001), and r = –0.515 (p = 0.001), respectively; DBP SD significantly correlated only in the period from day 1 to 3 (r = –0.550, p = 0.001).

Using a one-way regression analysis, we searched for the dependence of the grade of functional deficiency in patients in the acute period on day 21 on the variability of SBP on days 1–3, see Figure 8.

It was found that the degree of functional deficiency in patients in the acute period on day 21 depended on the variability of systolic BP on days 1–3, $R^2 = 0.304$, see Figure 8.

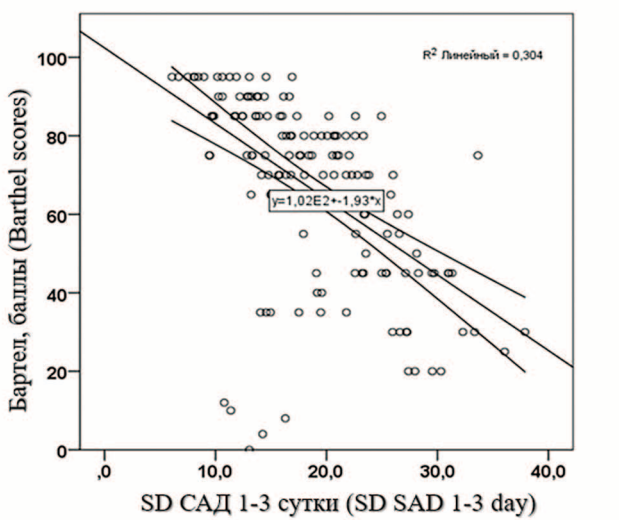

Figure 8. *Dependence of the degree of functional disorders in patients in the acute period of stroke on SD SBP on days 1– 3*

Note: SD SBP — standard deviation of systolic blood pressure during the day

Discussion

The results obtained demonstrate that BP variability during the acute period of stroke allows to identify the differences between mean systolic and diastolic blood pressure in stroke of different severity over time, and to demonstrate the significant role of BP variability in the functional consequences of stroke, defining the most informative corresponding terms.

Although hypertension has long been known to be a major vascular risk factor for cerebrovascular diseases and their clinical consequences, stroke, and dementia [13, 14, 16], randomized controlled trials (RCTs) and cohort studies provide ambiguous results as to whether high blood pressure (BP) and its management with antihypertensive agents contributes to the decrease in the risk of neurological deficits and functional impairment in stroke survivors. Inconsistent results increase the possibility that factors beyond absolute BP or target BP levels may be important in dealing with these issues.

Numerous empirical studies reveal that inter-measurement BP fluctuations, along with mean BP levels, have additional prognostic value for subclinical target organ damage, including brain [17, 18]. For example, A. E. Bennett et al. (2018) showed that increased blood pressure variability, as measured by standard

deviation (SD), coefficient of variation (CV), and serial variation (SV), predicts worse neurological outcomes measured by modified Rankin scale in patients with ischemic stroke. SV is the strongest and most consistent predictor of worse outcomes across all time intervals [33].

Once considered to be a background "noise" or a measurement error, intra-individual BP variation known as BP variability is important for predicting incident and recurrent stroke [34]. Higher BP variability has indirect effect on brain, including impaired cerebral autoregulation and temporary hypoperfusion [35].

Accumulated evidence suggests that blood pressure variability can contribute to end-organ damage causing coronary heart disease, stroke, and kidney damage, regardless of blood pressure (BP) levels. In addition to stroke, blood pressure variability is associated with a higher risk of cognitive impairment and dementia [36].

Several meta-analyses on BP variability have reported an association with acute stroke and transient ischemic attack (TIA), headache, atrial fibrillation, left ventricular mass index, mortality, cardiovascular outcomes, and multiple endpoints including stroke, mortality, and cardiovascular outcomes. Other systematic reviews and guidelines have focused on the statistical methods and technical aspects of the quantitative evaluation of BP variability [37].

In our paper, we show that the consequences of the acute period of stroke depend on BP level and its variability at the beginning of the acute period. On the first day of stroke, significantly higher mean SBP and SBP SD were registered with an increase in the stage of neurological deficit (after 8, 12, 16, and 20 hours). According to our study, BP variability during the acute stroke period is most closely related to the NIHSS score at the end of the acute period, as evidenced by the following values: SBP SD for a period of day 1 through 3 ($r = 0.725$, $p = 0.001$) and DBP SD ($r = 0.550$, $p = 0.001$), duration of AH ($r = 0.538$, $p = 0.001$), SBP SD for day 1 ($r = 0.487$, $p = 0.001$). It was established that more than 50 % probability of halving a lower NIHSS score (compared to baseline) is predicted if a patient's SBP SD on days 1–3 is below 12.4 mm Hg.

Correlation coefficients between the Barthel index and SBP SD on days 1–3 and on days 1–6 were as follows: $r = -0.551$ ($p = 0.001$) and $r = -0.515$ ($p = 0.001$), respectively; DBP SD significantly correlated with the Barthel index only in the period between day 1 and day 3 ($r = -0.550$, $p = 0.001$).

Conclusion

BP level and its variability during the acute phase of ischemic stroke allows predicting the severity of neurological deficit and the functional consequences of stroke during the recovery period.

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

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ХРОНИЧЕСКИЕ ЗАБОЛЕВАНИЯ ПЕЧЕНИ И COVID-19: БАЗА ДАННЫХ МНОГОПРОФИЛЬНОГО СТАЦИОНАРА

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Chronic Liver Diseases and COVID-19: Database of General Hospital

Резюме

Пациенты с хроническими заболеваниями печени (ХЗП) относятся к группе высокого риска инфицирования и тяжелого течения COVID-19 (Corona Virus Disease, коронавирусная инфекция 2019 года). **Цель**: создание базы данных (БД) пациентов с ХЗП, включающей анализ частоты выявления маркеров SARS-CoV-2, причин госпитализации, оценку 30-дневной летальности при наличии маркеров COVID-19 и в отсутствии инфекции. **Материалы и методы.** Проведено одномоментное ретроспективное обсервационное сравнительное исследование, результатом которого стало создание БД. Проанализированы 693 электронные медицинские карты пациентов с ХЗП различной этиологии, госпитализированных в терапевтические отделения ГКБ им. В.М. Буянова ДЗМ за период 01.04.2020–01.10.2021 гг. Анализ включал следующие параметры: пол, возраст, этиологию заболевания, причины госпитализации, наличие рибонуклеиновой кислоты (РНК) SARS-CoV-2 в мазке слизистой носа и ротоглотки, антител к SARS-CoV-2 иммуноглобулинов классов M, G (IgM, IgG), исход заболевания (30-дневная летальность). **Результаты.** Маркеры перенесенной новой коронавирусной инфекции (IgG) обнаружены у 268 (38,7 %), РНК SARS-CoV-2 выявлена у 67 (9,7 %). При анализе причин госпитализации установлено преобладание отечно-асцитического синдрома (64,5 %), нарастание печеночной энцефалопатии (31,6 %) и увеличение количества случаев тромбоза воротной вены (ТВВ) (8,9 %). При оценке 30-дневной летальности выявлены достоверные различия у пациентов с алкогольной болезнью печени (АБП), хроническими вирусными гепатитами (ХВГ) при наличии маркеров COVID-19 и в случаях их отсутствия. **Заключение.** Маркеры SARS-CoV-2 обнаружены у 335 (48,3 %) пациентов с ХЗП. Основная причина госпитализации — появление/нарастание отечно-асцитического синдрома, в том числе вследствие ТВВ. 30-дневная летальность в постковидном периоде достоверно выше при АБП в сравнении с пациентами без перенесенного COVID-19 (218 (34,9 %) и 300 (25,3 %), соответственно, p = 0,0246).

Ключевые слова: *COVID-19, хронические заболевания печени, база данных, летальность, алкогольная болезнь печени*

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Abstract
Patients with chronic liver diseases (CLD) are at high risk of infection and severe COVID-19 (Corona Virus Disease). **Aim:** to create a database of patients with CLD, including an analysis of the frequency of detection of SARS-CoV-2 markers, the causes of hospitalization, an assessment of 30-day mortality in the presence of COVID-19 markers and in the absence of infection. **Materials and methods.** A one-time retrospective observational comparative study was conducted, the result of which was the creation of a database. 693 electronic case hystories of patients with CLD of various etiologies hospitalized in the V.M. Buyanov State Clinical Hospital for the period 01.04.2020–01.10.2021 were analyzed. The analysis included the following parameters: gender, age, etiology of the disease, reasons for hospitalization, the presence of ribonucleic acid (RNA) SARS-CoV-2 in a smear of the nasal mucosa and oropharynx, antibodies to SARS-CoV-2 immunoglobulins of classes M, G (IgM, IgG), the outcome of the disease (30-day mortality). **Results.** Markers of past new coronavirus infection (IgG) were detected in 268 (38,7 %), SARS-CoV-2 RNA was detected in 67 (9,7 %). The analysis of the causes of hospitalization revealed the predominance of edematous ascitic syndrome (64,5 %), an increase in hepatic encephalopathy (31,6 %) and an increase in the number of cases of portal vein thrombosis (PVT) (8,9 %). When assessing the 30-day mortality, significant differences were found in patients with Alcohol-related liver disease (ARLD), chronic viral hepatitis in the presence of COVID-19 markers and in cases of their absence. **Conclusion**. SARS-CoV-2 markers were found in 335 (48,3 %) of patients with CLD. The main reason for hospitalization is the appearance /increase of edematous ascitic syndrome, including due to PVT. 30-day mortality in the postcovid period is significantly higher (p = 0,0246) in ARLD compared with patients without COVID-19 (218 (34,9 %) и 300 (25,3 %), respectively, p = 0,0246).

Key word: *COVID-19, chronic liver disease, database, mortality, alcoholic liver disease*

Conflict of interests
The authors declare no conflict of interests

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ACE2 — angiotensin-converting enzyme 2; AILDs — autoimmune liver diseases; ALD — alcoholic liver disease; CD147 — cluster of differentiation 147; CHB — chronic hepatitis B; CHC — chronic hepatitis C; CLDs — chronic liver diseases; COVID-19 — coronavirus disease 2019; CVH — chronic viral hepatitis; DB — database; DILI — drug-induced liver injury; EV — esophageal varices; GIB — gastrointestinal bleeding; HA — hepatitis A; HCC — hepatocellular carcinoma; LC — liver cirrhosis; MELD — model for end-stage liver disease; n — normal; NAFLD — non-alcoholic fatty liver disease; PVT — portal vein thrombosis; SARS-CoV-2 — severe acute respiratory syndrome coronavirus

Relevance

COVID-19 remains relevant due to its high prevalence and great importance for public health all around the world.

SARS-CoV-2 can infect various organs and systems of the body, including gastrointestinal tract and liver (epithelial cells, hepatocytes, cholangiocytes). SARS-CoV-2 spike protein targets are angiotensin-converting enzyme 2 (ACE2) and cluster of differentiation 147 (CD147). ACE2 is a widespread membrane-bound monocarboxypeptidase involved in the processing of many peptides, including angiotensin II. CD147 is a transmembrane glycoprotein. In the pathogenesis of SARS-CoV-2 infection, ACE2 and CD147 proteins function as “receptors” for the penetration of SARS-CoV-2 into the host cell [1, 2].

Chronic liver diseases (CLDs) are characterized by increased expression of hepatocyte ACE2, thereby potentially increasing the rate of SARS-CoV-2 entry into hepatocytes. S. Casey et al., 2020 [3], found a significant increase in ACE2 levels in the cases of liver cirrhosis (LC). Thus, the direct mechanism of liver damage in COVID-19 and CLDs is associated with the presence of a SARS-CoV-2 receptor in organ cells. This confirms virus detection in hepatocytes obtained during autopsy of patients with COVID-19 and LC [4].

In addition to the direct cytotoxic effect of the virus on cholangiocytes and hepatocytes, other mechanisms of liver damage are also distinguished: Immune-mediated damage as a result of a systemic inflammatory response; drug-induced damage (hepatotoxic effect of antibacterial and antiviral drugs, non-steroidal anti-inflammatory

Table 1. Characteristics of included patients

Etiology of CLD	Number of patients, n	Пол/Gender		Average age (years)
		Men (n)	Women (n)	
Alcoholic liver disease	420	240	180	50,4
Non-alcoholic fatty liver disease	24	7	17	56,4
Chronic hepatitis B, chronic hepatitis C	40	19	21	58,7
Autoimmune liver disease	24	3	21	54,3
Drug induced liver injury	19	9	10	57,3
Alcoholic liver disease + / Non-alcoholic fatty liver disease	65	31	34	56,4
Alcoholic liver disease + chronic hepatitis B, chronic hepatitis C	92	68	24	49,4
Rare diseases	9	3	6	48,4

Note: Rare diseases: cirrhosis of liver unspecified, combination of autoimmune hepatitis with HBV, HCV, Wilson-Konovalov's disease, glycogen storage disease, Crigler-Najjer syndrome 2

drugs, glucocorticoids, etc.); ischemia as a result of microangiopathy, microthrombosis with underlying endothelial dysfunction [5].

The multicenter cohort study using open online survey resulted in the development of the international registry of patients with CLDs and confirmed SARS-CoV-2 infection (n = 220,727). Patients with CLDs were found to have an increased risk of severe COVID-19 and poor outcome. When assessing 30-day mortality, the authors found that patients infected with SARS-CoV-2 had a 2.38-fold higher risk of adverse outcome than patients with LC with no COVID-19 [6].

Objective of our study: the development of a database (DB) of patients with CLDs, including the analysis of the frequency of SARS-CoV-2 markers detection, reasons for hospitalization, assessment of 30-day mortality depending on gender, age and etiology of liver disease.

Compliance with ethical standards: the study protocol No. 213 dated December 13, 2021, was approved by the local ethics committee of N. N. Pirogov Russian National Research Medical University (N. N. Pirogov Medical University of the Ministry of Health of Russia).

Materials and METHODS

To develop a DB, 693 electronic medical records of patients with CLDs of various etiology were analyzed; these patients were hospitalized into N. N. Buyanov City Clinical Hospital of Moscow Health Department (a multidisciplinary hospital that is not a COVID hospital) for the period 04/01/2020–10/01/2021. The range of liver diseases included the following: alcoholic liver disease (ALD), chronic viral hepatitis (CVH), non-alcoholic fatty liver disease (NAFLD), drug-induced liver disease (DILI), autoimmune liver diseases (AILDs), accumulation diseases (Wilson — Konovalov, glycogen liver disease). The DB also included 1 patient after liver transplantation for LC as an outcome of autoimmune hepatitis (AIH). Patients vaccinated against COVID-19 were not included in this study. The following parameters were evaluated: gender, age, etiology of the disease, reasons for hospitalization, presence of SARS-CoV-2 RNA in nasal and oropharyngeal mucosal smear and antibodies to SARS-CoV-2 immunoglobulins of classes M, G (IgM, IgG), disease outcome (30-day mortality).

Statistical processing was carried out using Statistica 13.0 and Python3 software. Nonparametric statistical methods were used: for the analysis of qualitative features — $\chi 2$ test and Fisher's exact test; for comparing two independent values — the Mann — Whitney test, as well as the Spearman's correlation coefficient (Spearman's r).

Results

Comparing the data on the detection of new cases of COVID-19 in Moscow and the detection of SARS-CoV-2 RNA in patients with CLDs in hospital for the same period of time revealed moderate positive correlation (Spearman's r — 0.56) (Figure 1).

The markers of the past novel coronavirus infection were found in 268 patients (38.7 %); SARS-CoV-2 RNA was detected on days 1–7 of hospitalization in 67 (9.7 %) patients. The etiology of CLDs in patients included in the sample (n = 335) is presented in Figure 2.

Detection rate of SARS-CoV-2 RNA, past infection markers (IgG), as well as 30-day mortality in these groups of patients with CLDs of various etiologies is presented in Table 2.

The group of patients with ALD and markers of past infection (SARS-CoV-2 IgG) was the largest one (218/270). In this group, alcoholic hepatitis (AH) was diagnosed in 23 (10.6 %) cases, severe AH with cirrhosis — in 53 cases (24.3 %), and decompensated LC — in 142 cases (65.1 %). The main complications of ABP are shown in Figure 3.

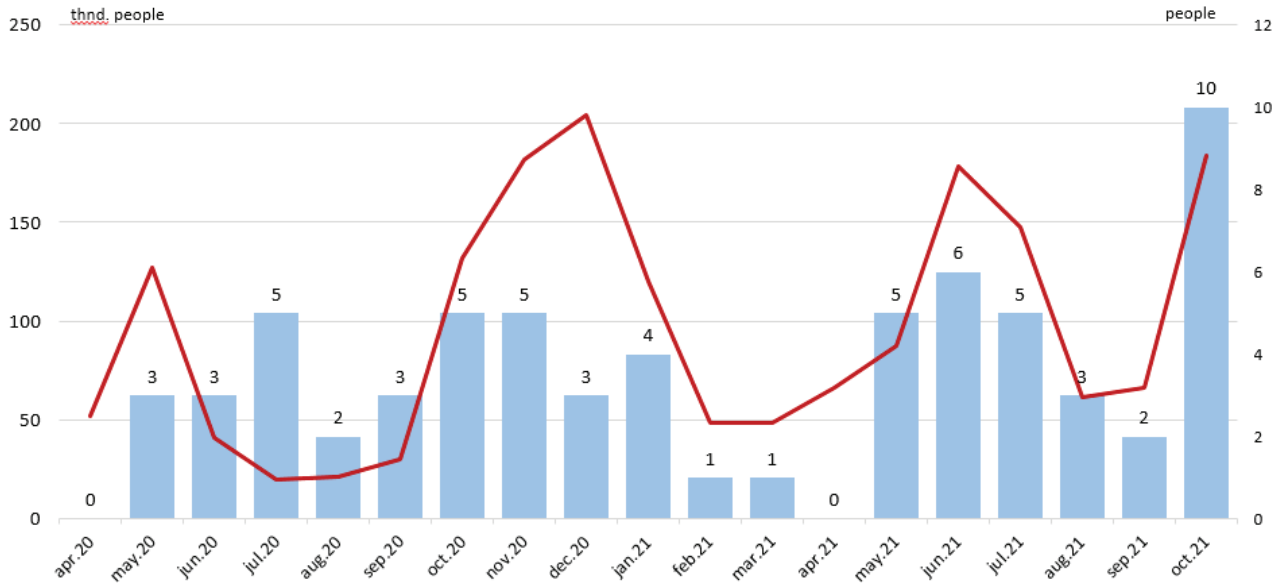

Figure 1. *Number of new cases COVID-19 in Moscow, thnd people, and number of patients with CLD + RNA SARS-CoV-2*
Columns (light blue) — number of patients with RNA SARS-CoV-2
Red line — number of new cases COVID-19 in Moscow, thnd people [7]

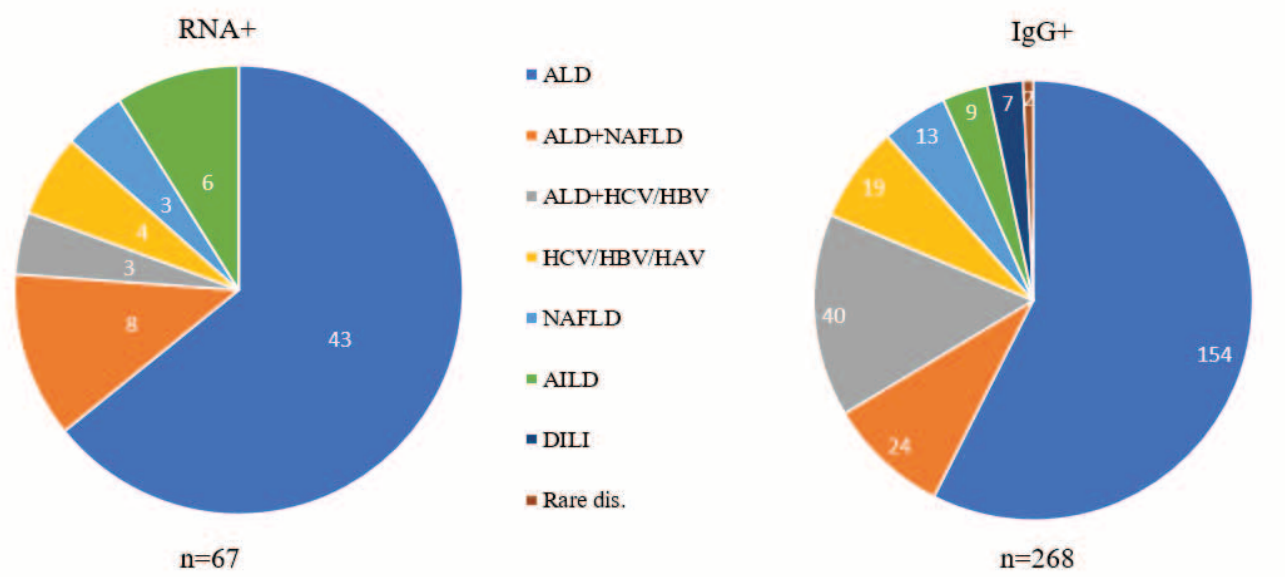

Figure 2. *Etiological structure of chronic liver diseases (CLD) for patients with COVID-19*
Note: Rare diseases: cirrhosis of liver unspecified, combination of autoimmune hepatitis with HBV, HCV; ALD — alcoholic liver disease; NAFLD — non-alcoholic fatty liver disease; HBV — chronic hepatitis B; HCV — chronic hepatitis C; AILD — autoimmune liver disease; DILI — drug induced liver injury

Table 2. *COVID-19 markers, 30-day mortality in CLD of various etiologies*

Etiology of CLD	n	Patients with CLD without markers COVID-19		RNA SARS-CoV-2			IgG SARS-CoV-2		
		n	30-day mortality (%)	n	30-day mortality (%)	P1	n	30-day mortality (%)	P2
ALD	570	300/570	25,3	52/570	59,6	<0,0001	218/570	34,9	0,025
NAFLD	40	18/40	0	3/40	0	1,0	19/40	5	1,0
HBV, HCV	132	66/132	7,6	7/132	42,9	0,0021	59/132	8,5	0,818
AILD	24	9/24	11,1	6/24	0	1,0	9/24	22,2	1,0

Note: P1 — difference between CLD patients without COVID-19 markers and those with SARS-CoV-2 RNA; P2 — difference between CLD patients without COVID-19 markers and those with SARS-CoV-2 IgG

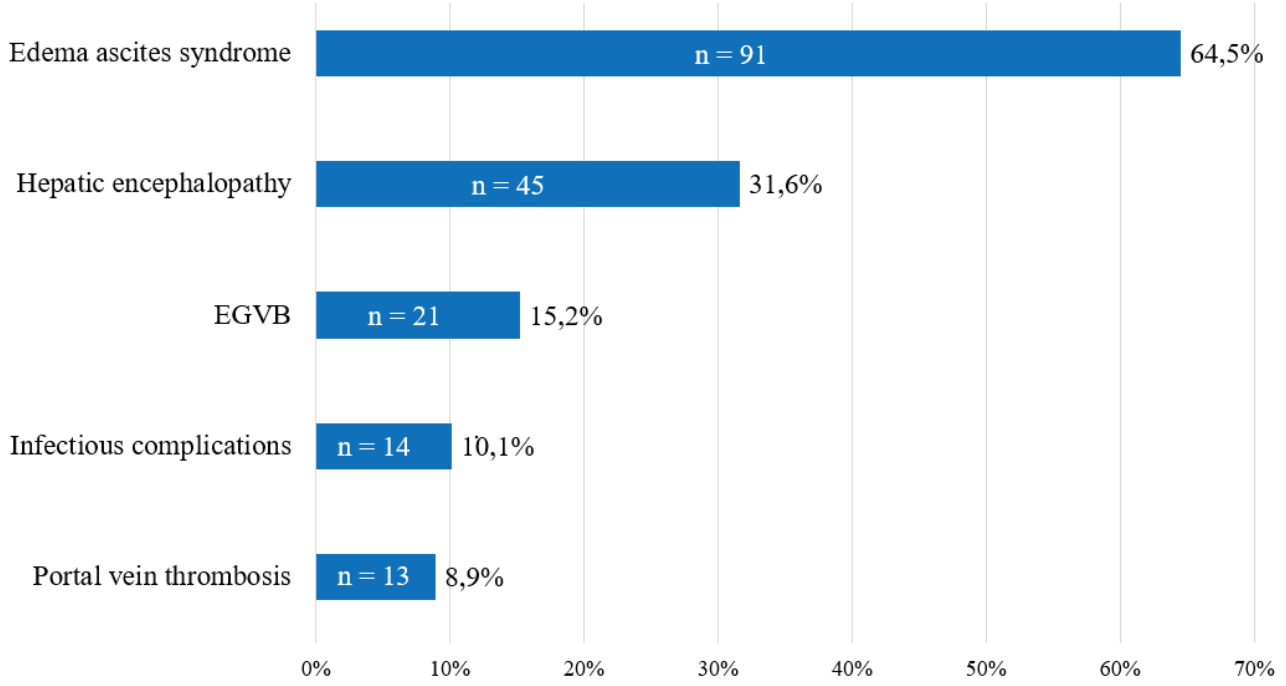

Figure 3. *Complications of cirrhosis in ALD*
Note: EGVB — esophagogastric variceal bleeding

The assessment of 30-day mortality revealed significant differences in patients with ALD and CVH in the presence of COVID-19 markers and in cases of their absence. 30-day mortality in patients with NAFLD, AILDs with the presence of SARS-CoV-2 RNA/IgG was also higher (Table 2), however, no significant differences were found due to their small number.

In the patients of the analyzed group, 11 (1.6 %) cases of hepatocellular carcinoma (HCC) were found: 8 (72.7 %) cases in the outcome of CVH; 2 (18.1 %) — with ABP; 1 (9.1 %) — with a combination of ABP + NAFLD.

Results and Discussion

The results presented demonstrate the differences in the course and outcomes of CLDs with underlying COVID-19.

When analyzing the causes of hospitalization, special attention should be paid to the prevailing edematous-ascitic syndrome, as well as to increased number of the cases of portal vein thrombosis (PVT).

Thromboses of various locations are one of the frequent complications of novel coronavirus infection, both during acute infection phase and in the post-COVID period. According to a meta-analysis, the incidence of thrombotic complications in COVID-19 ranges from 7 to 40 % [8]. The most common locations of thrombosis are deep veins of lower legs that in several cases can be complicated with the development of pulmonary embolism.

According to the American Association for the Study of Liver Diseases [9], the incidence of PVT among patients with LC with no COVID-19 is 0.6–26.0 % depending on its Child-Pugh severity class. However, the incidence of PVT in the post-COVID period is not assessed yet. According to our study, it was 8.9 %.

The second most common reason for hospitalization was the onset/exacerbation of hepatic encephalopathy. There are published data on the correlation of hyperammonemia with the severity of COVID-19 and inflammatory markers (C-reactive protein, leukocytes, ferritin); it can be used as a predictor of the severity of new coronavirus infection [10].

The patients with CLDs, especially at the stage of cirrhosis, are more susceptible to infections, including COVID-19, due to their systemic immunodeficiency. When comparing the data obtained regarding the frequency of detecting COVID-19 markers in hospital patients and in the general population of Moscow as of October 1, 2021 [7], the higher frequency was established in hospital patients infected with CLDs (38.7 % vs 12.9 %, respectively). It should be emphasized that patients with different chronic diseases belong to the risk group due to frequent hospitalizations, as well as to numerous contacts with possible sources of infection (other patients, medical staff, pharmacists) in outpatient healthcare system.

According to the results obtained by T. Marjot et al., 2021 [11], the patients with LC had the increased risk of adverse outcomes when infected with SARS-CoV-2. Mortality in the group of LC patients with COVID-19

differed depending on LC stage according to the Child-Pugh scale: it was 19 % in class A cirrhosis (n = 33), 35 % in class B (n = 44), 51 % in class C (n = 46). In this study, the main cause of death was COVID-19-associated lung injury (71 %, n = 87), however, 19 % (n = 23) of deaths were due to liver cirrhosis-related complications. The analysis of these cases also demonstrated a significant impact of the coronavirus infection on the course of CLDs. The incidence of acute liver decompensation in this cohort was 46 % (n = 179).

The DB presented demonstrates a high incidence of adverse outcomes in patients with CLDs with novel coronavirus infection, as well as higher mortality in the post-COVID period. This dependence can be reliably traced in the group of patients with ALD.

There are published data on the immunomodulatory effect of the long-term consumption of alcohol in high doses that, when an individual is infected with SARS-CoV-2, can contribute to the development of other infections, as well as of the acute respiratory distress syndrome [12]. When comparing the outcomes in patients with alcoholic LC and in patients with LC of mixed origin (alcoholic + CHC/CHB), mortality in the post-COVID period was higher in the ALD group (Figure 4) and amounted to (42.2 % and 5.0 %, respectively).

In addition, the analysis of data from the international registry [11] established a higher incidence of adverse outcomes in ALD during COVID-19 in comparison with CLDs of other etiologies.

Among the patients with CHC and CHB after novel coronavirus infection, the 30-day mortality rate was higher (8.5 %) than in patients with viral CLDs with no coronavirus infection (7.6 %), however, it was significantly lower than in the patients with ALD (34.9 %). However, there were no significant differences in this parameter in patients with CHC, apparently due to the small size of the sample. Meanwhile, A. A. Butt et al., 2021 [13], obtained similar results for CHC with and without COVID-19; significant differences in 30-day mortality were revealed only at the cirrhosis stage.

According to A. A. Saryglar et al., 2022 [14], the patients with CHB (n = 46, including 16 patients at cirrhosis stage) who received antiviral therapy with entecavir demonstrated a mild course of novel coronavirus infection in most cases (87 %). No fatal outcomes were registered; this fact is also consistent with the data obtained by J. Zhu et al., 2021 [15]. However, the mechanism of the possible protective effect of HBV AVT on the signs of COVID-19 was not clarified.

However, considering the specific features of COVID-19 course in elderly people vaccinated against hepatitis A (HA) that was characterized by extremely low mortality (1.8 %), it was suggested that immunity against HA can provide protection against COVID-19 [16]. The presented literature data and our own observations revealed "specific" interviral interactions in CVH and GA [17] that require further investigation.

The mortality in the group of patients with AILDs in the post-COVID period did not differ from this parameter in patients with no COVID-19 markers; this fact was also demonstrated in the study by T. Marjot et al., 2021 [11].

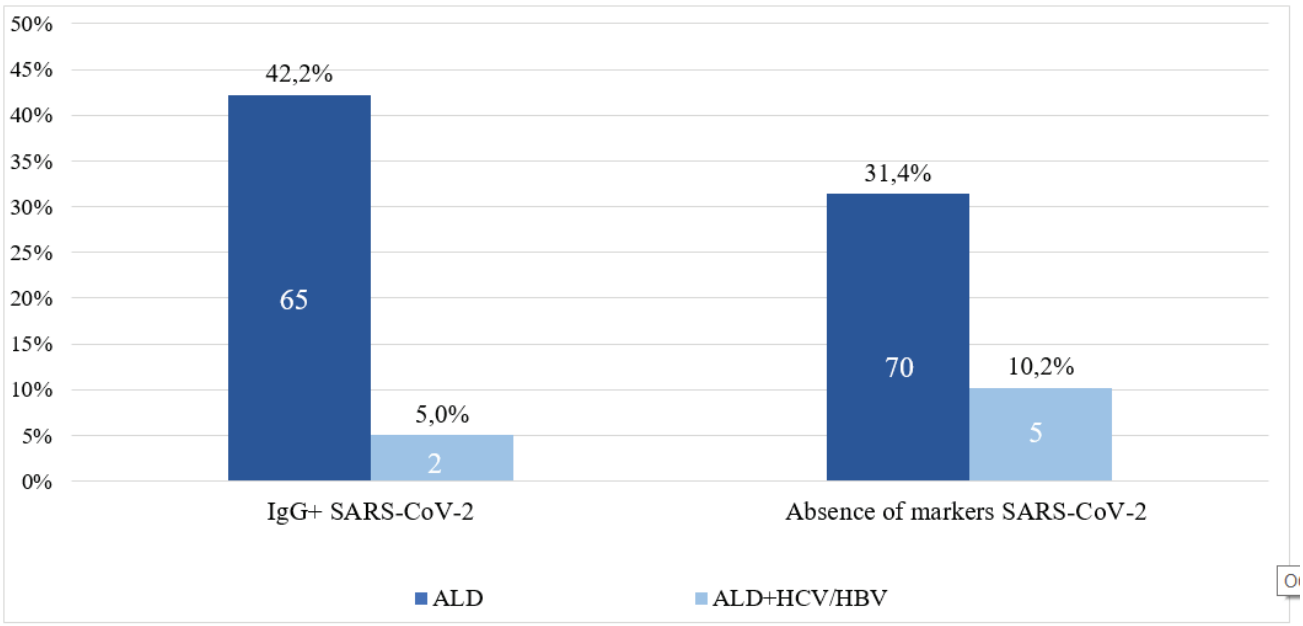

Figure 4. *Mortality of ALD and ALD+HBV/HCV*
Note: ALD — alcoholic liver disease; HBV — chronic hepatitis B; HCV — chronic hepatitis C

We have diagnosed 11 cases of HCC. There are reports of the increased mortality in this group of patients [18]. Meanwhile, it is not excluded that the increased number of adverse outcomes due to HCC may be associated with a delay in the start of anticancer treatment in the context of the redistribution of healthcare system resources during the pandemic. However, the question of the oncogenic effect of SARS-CoV-2 and the development of malignant tumors remains open.

The presented DB and the analysis of several published studies emphasize that CLDs patients are at risk for severe COVID-19 that requires active preventive measures, including mandatory vaccination. Thus, according to J. Ge et al., 2022 [19], vaccination reduced 30-day mortality in patients with LC and COVID-19 (n = 8,218) by 66 %. A. Moon et al., 2022 [20], also mentioned a significant decrease in mortality in vaccinated patients with CLDs, as well as the fact that such patients needed no mechanical ventilation.

Conclusion

Direct cytotoxic effect of SARS-CoV-2 on cholangiocytes and hepatocytes, as well as other mechanisms of negative effect on the course of CLDs, were established. Significant increase in the number of thrombotic complications, including PVT, is observed. The mortality in the patients with CLDs and SARS-CoV-2 RNA or IgG is significantly higher, especially in cases of ALD (59.6 % and 34.9 %, respectively, $p < 0.0001$ and $p = 0.0246$).

There is no idea about the interaction and mutual influence of SARS-CoV-2 and other hepatotropic viruses, as well as about the mechanisms that contribute to the development of autoimmune and oncological diseases. The repeated cases of infection do not exclude the possibility of the long-term persistence of SARS-CoV-2 in human body. It is necessary to continue the study of epidemiological, clinical and pathogenetic specific features of CLDs in patients co-infected with hepatitis viruses and SARS-CoV-2, as well as to perform the follow-up for this cohort in the post-COVID period.

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ИНТЕГРАЛЬНАЯ ОЦЕНКА ВНУТРИПЕЧЕНОЧНОГО КРОВОТОКА — НОВОЕ НАПРАВЛЕНИЕ В НЕИНВАЗИВНОЙ ДИАГНОСТИКЕ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ ПЕЧЕНИ

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Integral Assessment of Intrheateral Blood Flow — a New Direction in Non-Invasive Diagnostics of Chronic Liver Diseases

Резюме

Цель исследования. Оценить чувствительность, специфичность и диагностическую точность способа неинвазивной дифференциальной диагностики заболеваний печени методом полигепатографии. **Материалы и методы.** Методом случайной выборки было обследовано 45 пациентов (28 женщин, 17 мужчин). Всем пациентам для определения нарушений внутрипеченочной микроциркуляции при первичном обращении была проведена полигепатография. На основании выявленных изменений внутрипеченочной гемодинамики на основе морфофункциональной гемодинамической модели было сделано заключение о нарушении внутрипеченочного кровотока и высказано предположение об этиологии и стадии заболевания печени. В последующем верификация диагноза заболеваний печени осуществлялась после детального изучения общепринятых в гепатологии клинико-лабораторных, инструментальных и морфологических данных. У 5 (11,1%) исследуемых была проведена пункционная биопсия печени по методу Menghini. **Результаты.** На основании полученных данных о нарушении внутрипеченочной микроциркуляции при проведении полигепатографии все исследуемые были разделены на три группы. I группу составили пациенты с нарушенным венозным притоком, во II группу вошли пациенты с нарушенным артериовенозным притоком, в III группу — с нарушенным венозным оттоком. *Полученные данные полигепатографии (ПГГ) были сопоставлены с результатами клинико-лабораторных, инструментальных и морфологических данных. Определена высокая чувствительность, достаточная специфичность и точность метода полигепатографии в диагностике хронических заболеваний печени.* **Заключение.** Проведенные исследования свидетельствуют, что ПГГ — простой, доступный и необременительный для пациента метод обследования, который позволяет неинвазивно оценить локализацию нарушений внутрипеченочного кровотока, и с определенной долей вероятности предположить этиологический фактор заболевания и стадию заболевания. Учитывая специфичность изменений гемодинамики печени в зависимости от этиологического фактора и стадии заболевания, исследование внутрипеченочной гемодинамики методом полигепатографии может быть рекомендовано в качестве скринингового метода при обследовании пациентов с заболеваниями печени, что позволит сократить время диагностического поиска.

Ключевые слова: *внутрипеченочная гемодинамика, внутрипеченочная микроциркуляция, полигепатография, хронические заболевания печени, аутоиммунные заболевания печени, стеатогепатит, вирусный гепатит, диагностика хронических заболеваний печени*

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Конфликт интересов

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

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Abstract

Purpose of the study. To assess the sensitivity, specificity and diagnostic accuracy of the method for non-invasive differential diagnosis of liver diseases by polyhepatography. **Materials and methods.** A random sampling method examined 45 primary patients. Polygepatography was performed on all patients to detect disorders of intrahepatic microcirculation during primary contacting. Based on the detected changes in intrahepatic hemodynamics and based on the morphofunctional hemodynamic model, a conclusion was made about the violation of intrahepatic blood flow and an assumption was made about the etiology and stage of liver disease. Subsequently, the diagnosis of liver diseases was verified after a detailed study of clinical-laboratory, instrumental and morphological data generally accepted in hepatology. Puncture liver biopsy by the Mancini method was performed in 11.1% of the subjects. **Results.** All subjects were divided into three groups based on the data obtained on impaired intrahepatic hemodynamics during polyhepatography (PHG). The group I consisted of patients with impaired venous inflow, the group II included patients with impaired arteriovenous inflow, and group III — with impaired venous outflow. The obtained polyhepatographic data were compared with the results of clinical-laboratory, instrumental and morphological data. The high sensitivity, sufficient specificity and accuracy of the polyhepatography method in the diagnosis of chronic liver diseases have been determined. **Conclusion.** The studies carried out indicate that PHG is a simple, accessible and not burdensome examination method for the patient, which makes it possible to assess the localization of intrahepatic blood flow disorders, and, with a certain degree of probability, to assume the etiological factor of the disease and the stage of the disease. Given the specificity of changes in liver hemodynamics, depending on the etiological factor and stage of the disease, assessment of intrahepatic hemodynamics by polyhepatography can be recommended as a screening method for examining patients with liver diseases, which will shorten the diagnostic search time.

Key words: *intrahepatic hemodynamics, intrahepatic microcirculation, polyhepatography, chronic liver disease, autoimmune liver diseases, steatohepatitis, viral hepatitis, diagnosis of chronic liver diseases*

Conflict of interests

The authors declare no conflict of interests

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AILDs — autoimmune liver diseases, ALP — alkaline phosphatase, CIC — circulating immune complexes, CLDs — chronic liver diseases, EGDS — esophagogastroduodenoscopy, ESR — erythrocyte sedimentation rate, HSCs — hepatic stellate cells, PHG — polyhepatography

Introduction

Chronic liver diseases (CLDs) are a serious problem of the present-day health care. This is due not only to their prevalence, but also to mortality associated with the development of liver cirrhosis and hepatocellular carcinoma [1].

Inapparent and polymorphous clinical presentation of CLDs cause certain difficulties in their timely diagnosis, lead to the progression of the pathological process and to the development of life-threatening complications [2].

Experimental and clinical data demonstrate that vascular failure precedes the parenchymal one and is observed along with a slightly altered functional state of liver. According to literature sources, hemodynamic disorders are observed in 94% of patients with CLDs. In the structure of the overall mortality in such patients, hemodynamic disorders account for up to 60% [3].

It is essential that the morphofunctional heterogeneity of hepatocytes determines the different nature of intrahepatic blood flow disorders depending on the etiology and stage of liver disease. It is known that a hemodynamic block in the periportal zone (the first zone) of hepatic acinus most often develops in autoimmune or viral diseases, while in the patients with non-alcoholic fatty liver disease or alcoholic hepatitis it takes place in the area of central hepatic veins (the third zone of hepatic acinus). Moreover, recent studies confirm the significant

role of hepatic stellate cells (HSCs) in the pathogenesis of liver diseases. HSCs regulate blood flow at the level of hepatic sinuses and are the main source of collagen production in liver when they interact with fibroblasts. Activated HSCs and fibroblasts exhibit profibrogenic properties due to their ability to synthesize substances that inhibit the breakdown of fibrin and substances that promote the synthesis of fibrous matrix proteins (type I collagen, fibronectin, hyaluronic acid). The development of fibrogenesis processes in liver is one of the important steps in the pathogenesis of chronic hepatitis. In turn, it is known that liver structure is not the result of a rigid anatomical organization, however, it is developed under the effect of functional hemodynamic factors, and the heterogeneity of intrahepatic blood flow disorders determines the mosaic development of liver fibrosis. Intrahepatic blood flow disorders trigger a cascade of metabolic and neurohumoral processes leading to changes in central hemodynamics; such changes further exacerbate liver microcirculation disorders and contribute to the progression of the pathological process with the development of portal hypertension, fibrosis and reorganizing of liver architecture. Besides, the intrahepatic blood flow pattern depends on the effectiveness of the biliary system function and lymph flow. In view of the above, it can be assumed that the diagnosis of CLDs can be based on the identification of intrahepatic blood flow and central hemodynamic disorders; timely identification and management of the identified disorders can increase the effectiveness of pathogenetic therapy and significantly reduce the risk of liver fibrosis [4].

The process of liver regeneration is considered extremely promising. It is known that in the experiment with resection of 50–70 % of liver, its initial weight and dimensions restored in 10–14 days [5]. However, in a pathological process, impaired intrahepatic blood flow does not provide close interaction between blood and hepatocytes, thus impairing their metabolism and resulting in the development of less blood-requiring connective tissue together with changes in the liver architecture. Therefore, regardless of the disease etiology, impaired intrahepatic hemodynamics is an important part in the CLD pathogenesis. Thus, it seems extremely important to have an available non-invasive technique for the control of changes in liver hemodynamics. However, this field of hepatology has significant limitations due to the lack of an affordable technique for assessing the state of intrahepatic blood flow [6].

This problem can be solved with the help of a simple, affordable and non-invasive method — polyhepatography. Polyhepatography (PHG) is a technique for assessing liver hemodynamics based on the simultaneous analysis of several rheograms (blood filling curves) of the intrahepatic area and central pulse curves [4].

Study Objective

To assess the sensitivity, specificity and diagnostic accuracy of the polyhepatography technique for non-invasive diagnosis of chronic liver diseases.

Materials and Methods

This study was carried out in the Research Laboratory of Innovative Methods of Functional Diagnostics of the I. I. Mechnikov North-Western State Medical University of the Ministry of Health of Russia; for this study 45 patients (28 females, 17 males) were randomly examined; the average age of the patients was (49.0 ± 8.4) years. During their initial presentation, the patients complained of various signs of asthenic vegetative syndrome: general weakness (97.7 %, n = 44), rapid fatigability (95.5 %, n = 43). Pain syndrome (heaviness and/or discomfort in right hypochondrium) was reported by 42 (93.3 %) subjects. Patients also complained of different signs of dyspeptic syndrome: heartburn (64.4 %, n = 29), burping (46.7 %, n = 21), bloating (37.7 %, n = 17), loose stools (8.9 %, n = 4), tendency to constipation (2.2 %, n = 1). Cholestasis syndrome in the form of pruritus was mentioned by 7 (15.5 %) subjects.

All patients underwent polyhepatography with functional hemodynamic tests (at the height of inhalation and with nitroglycerin) to identify changes in the state of intrahepatic blood flow during the initial visit; the results of these tests allowed to make a conclusion about persistent or functional hemodynamic disorders of arteriovenous inflow and venous outflow in liver and spleen. Based on the results of this examination, a conclusion was made on the state of intrahepatic hemodynamics, severity and localization of hemodynamic disorders, the presence of liver fibrosis according to METAVIR score, and an assumption was made about the etiology of the disease. PHG was carried out using the Valenta+ hardware and software complex with the modified set of devices and programs (NEO Research and Production Company, St. Petersburg). A morphofunctional hemodynamic model of liver was taken as the basis of the algorithm for interpreting PHG results [4]. Based on the developed model and PHG results, an assumption was made about the etiology of liver disease [7].

Subsequent verification of the diagnosis of CLD was carried out after a thorough analysis of the results of clinical and instrumental examinations and laboratory tests. To verify the etiology of the disease, serological and molecular genetic markers of viral liver damage were determined: hepatitis A IgM antibodies (Anti-HAV IgM), hepatitis A IgG antibodies (Anti-HAV IgG), hepatitis B surface antigen (HBsAg), hepatitis B surface antigen protective antibodies (HBsAb), hepatitis B

e-antigen (HBeAg), hepatitis B e-antigen antibodies (HBeAb), nuclear core antigen antibodies (HBcAb), hepatitis B virus DNA (HBV DNA); antibodies to hepatitis C virus (anti-HCV), hepatitis C virus DNA (HCV RNA). To exclude autoimmune damage, patients were screened for autoimmune liver diseases: smooth muscle antibodies (SMA), liver-kidney microsomal antibody type 1 (LKM1), antimitochondrial antibodies (AMA), antinuclear antibodies (ANA). If antimitochondrial antibodies to M2 subtype antigen (AMA M2) and LKM1 were detected, the antibodies to the autoantigens of liver diseases were assessed (antibodies to the pyruvate-decarboxylase complex of mitochondria AMA M2 (PDC), antibodies to liver cytosolic antigen type 1 (LC-1), antibodies to soluble liver/pancreas antigen (SLA/LP), antibodies to Sp100 nuclear granule proteins and PML protein, antibodies to integral nuclear membrane protein gp210). In addition, the presence of circulating immune complexes (CIC), as well as class A, M, G immunoglobulins was determined. All patients underwent general clinical tests: complete blood count, urinalysis with a qualitative reaction to urobilin and bile pigments, coprogram, and fecal occult blood test by immunochemical method. Biochemical tests included assessment of total protein and protein fractions, prothrombin index, concentration of bilirubin and its fractions, levels of serum enzymes (alanine aminotransferase and aspartate aminotransferase), alkaline phosphatase (AP), amylase, glucose, blood lipid profile, urea, electrolytes (potassium, calcium, sodium). Ultrasound examination of abdominal organs was performed to assess the size and structure of the parenchyma of liver, pancreas, gallbladder, spleen, and portal vein. Esophagogastroduodenoscopy was performed to detect signs of portal hypertension — esophageal varices and gastric cardia. Five (11 %) patients underwent a percutaneous liver biopsy according to the Menghini technique. During the histological analysis of biopsy samples, the activity of inflammatory process and the stage of liver fibrosis were assessed using semiquantitative scales developed by R. J. Knodell et al. (1981), as well as fibrosis severity according to METAVIR score. Clinical diagnosis was defined on the basis of ICD-10 classification.

Statistical processing of values obtained was carried out using Statistica 10.0 software package. In cases of the normal distribution of sample data, results were presented as the mean and standard deviation (M ± SD); in case of non-compliance with the normal distribution, as a median (Me), and lower and upper quartiles (Q25 %, Q75 %). When comparing independent groups, the Mann — Whitney U test or Kolmogorov — Smirnov test was used for non-parametric values, and Student's t-test for parametric values [8, 9]. Differences in the results of the comparison of samples were considered significant at $p < 0.05$. Specificity, sensitivity, likelihood ratios, and predictive ability of the detected diagnostic aspect were determined using two-row by two-column tables (contingency tables). Evaluation of the information value of PHG results for each of the detected signs of patient's condition was calculated using the corresponding formulas [10, 11].

Results

Based on the obtained PHG data on impaired intrahepatic hemodynamics, all studied patients were divided into 3 groups. Group I included patients with impaired venous inflow (Figure 1); group II included patients with impaired arteriovenous inflow (Figure 2); and group III included patients with impaired venous outflow (Figure 3). If a patient had both inflow and outflow impairments, the prevailing one was considered.

According to the results of clinical examinations and laboratory tests in group I (n = 15), complete blood count revealed elevated ESR (erythrocyte sedimentation rate); blood biochemistry test demonstrated the presence of cytolysis and cholestasis syndromes (Table 1).

According to liver ultrasound: hepatomegaly (54 %, n = 8), diffuse changes in liver parenchyma (67 %, n = 10), gallbladder deformity (47 %, n = 7), diffuse changes in pancreas (74 %, n = 11). Esophagogastroduodenoscopy (EGDS) revealed the signs of chronic gastroduodenitis in 47 % (n = 7) cases, erosive gastritis in 14 % (n = 2), cardia insufficiency in 27 % (n = 4). Viral hepatitis was confirmed in 67 % of cases (n = 10): four patients had viral hepatitis B, and six patients had viral hepatitis C. One patient had increased IgG anti-HAV level with negative IgM anti-HAV; these results were regarded as past viral hepatitis A. In three patients with negative markers of hepatitis viruses, there was increased titer of antinuclear factor and the presence of antimitochondrial antibodies that indicated the presence of an autoimmune liver disease. Morphological changes in liver biopsy samples of patients with viral hepatitis were characterized by the presence of "ground glass" hepatocytes, "sanded" nuclei, lymphoid infiltration of portal tracts, less often — fatty degeneration of hepatocytes. The degree of necroinflammatory response according to Knodell score was 4–5 points, liver fibrosis according to METAVIR was F 1–2.

Laboratory tests in group II (n = 13) revealed cytolytic and cholestatic syndromes, however, the increase in transaminases and cholestasis enzymes was more significant in group II (Table 1). According to the liver ultrasound, the following changes were revealed: hepatomegaly (47 %, n = 6), splenomegaly (39 %, n = 5), diffuse changes in liver parenchyma (85 %, n = 11), gallbladder

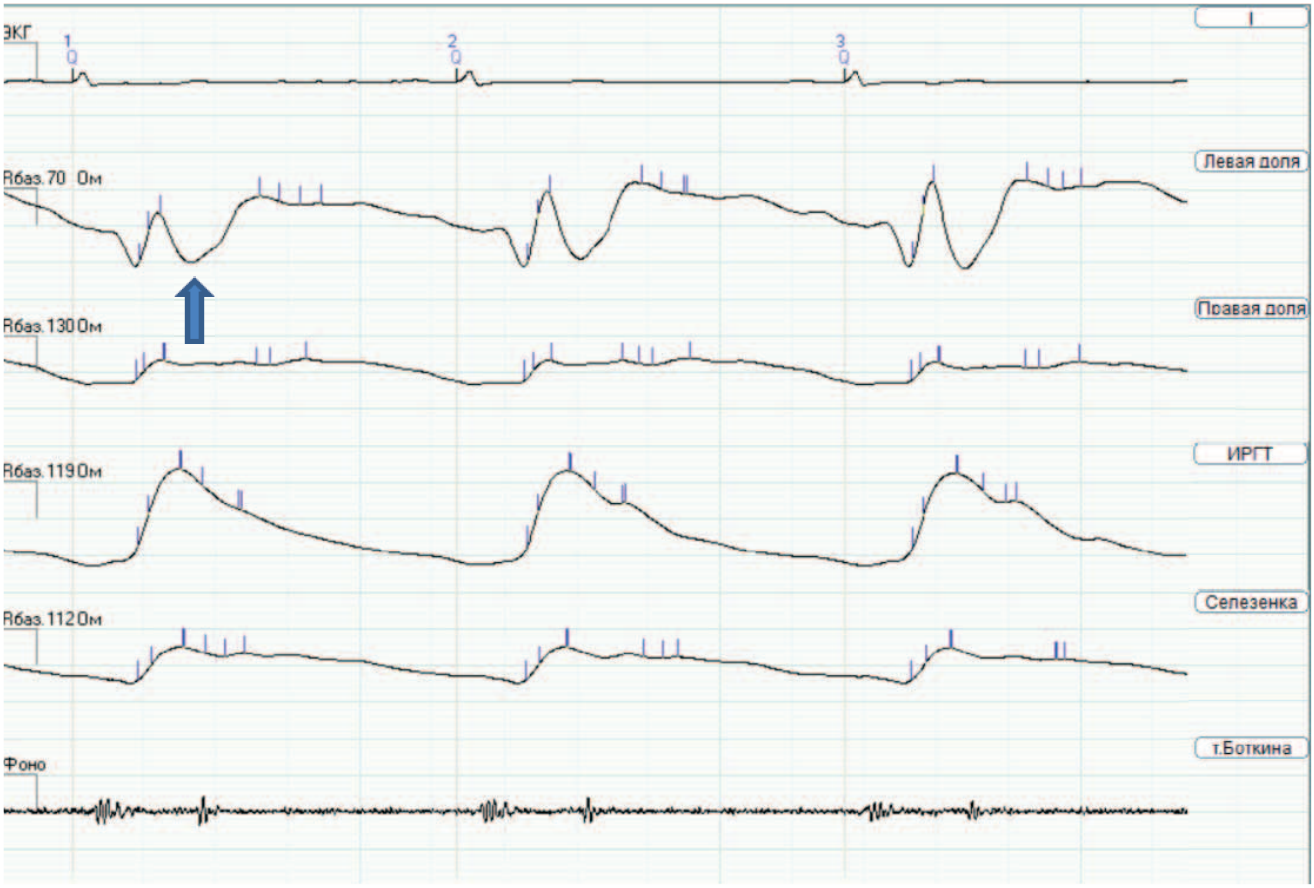

Figure 1. *Polyhepatogram. Lying background. Severe venous inflow disorders in the left lobe of the liver. The arrow indicates the zone of violation*

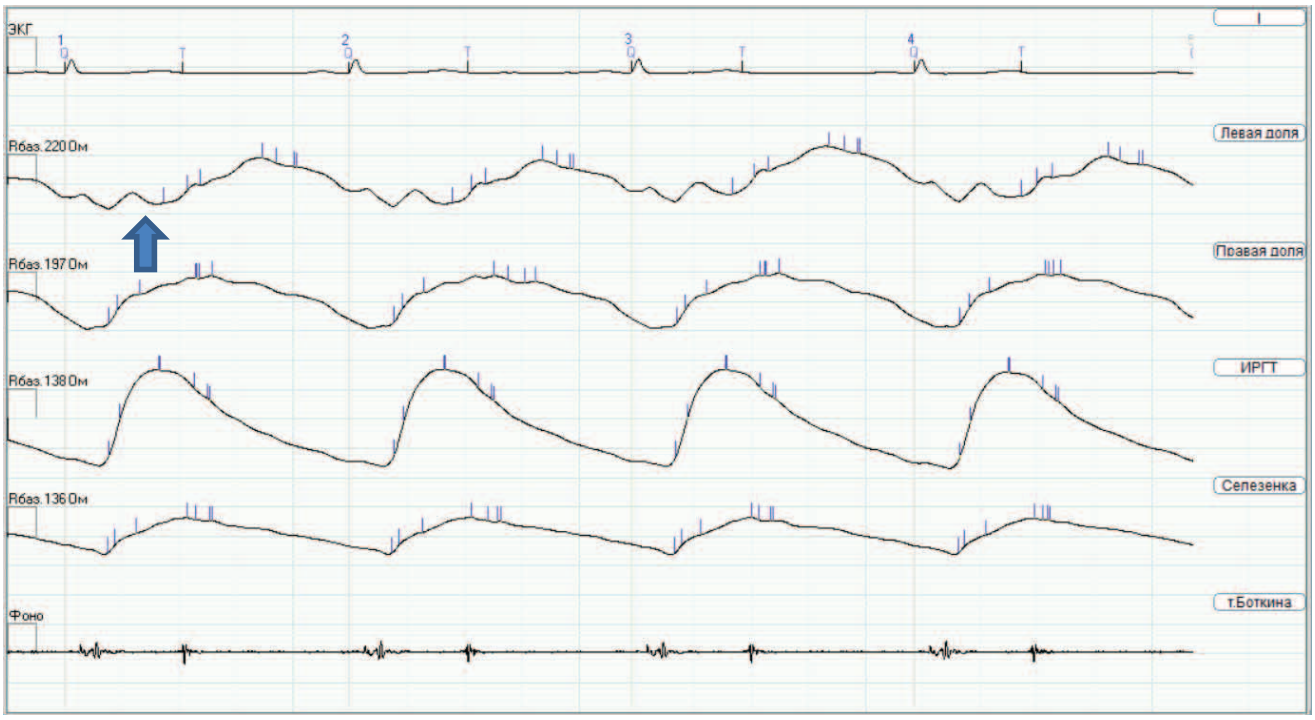

Figure 2. *Polyhepatogram. Lying background. Arteriovenous inflow disorders mainly in the left lobe of the liver. The arrow indicates the zone of violation*

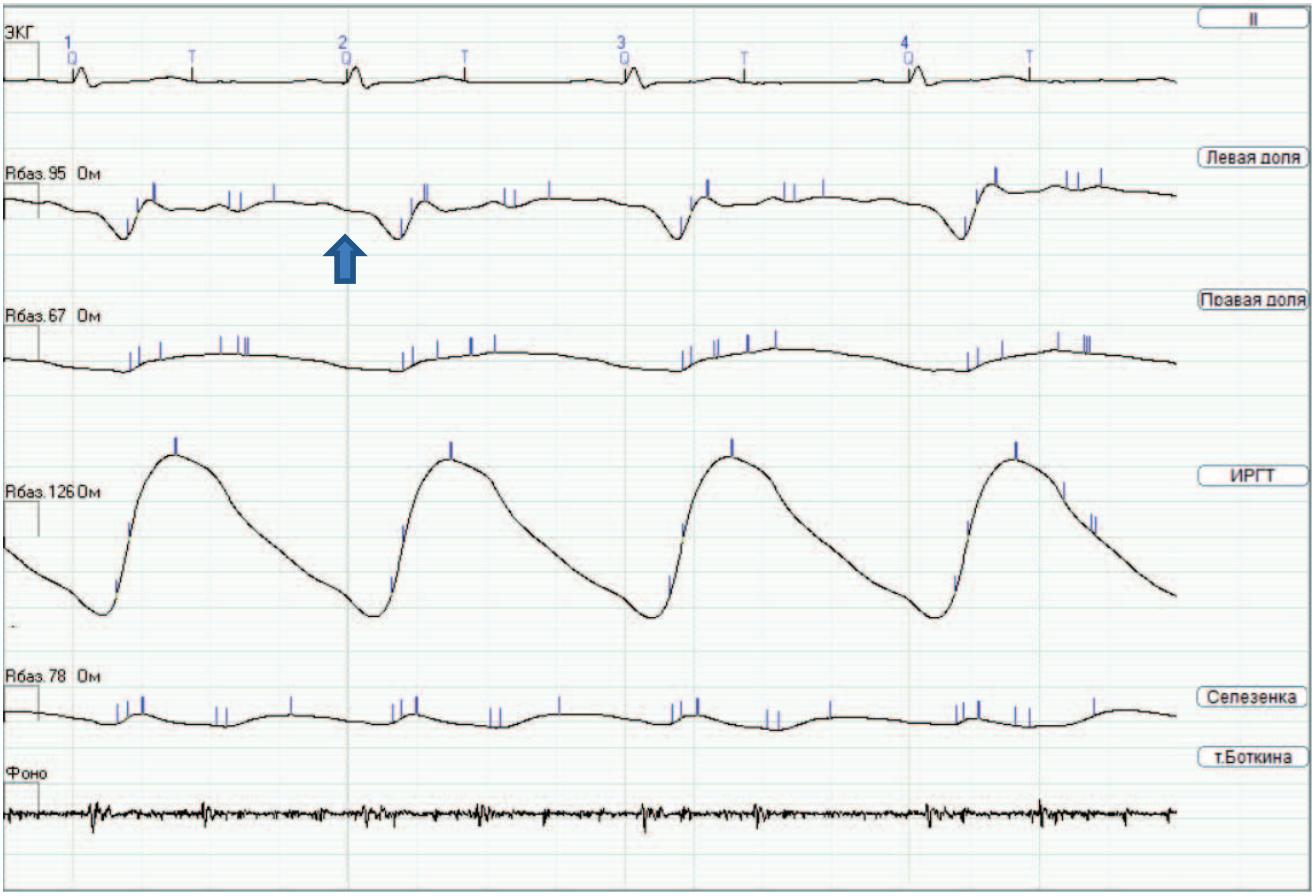

Figure 3. *Polyhepatogram. Lying background. Signs of impaired venous outflow from the liver. The arrow indicates the zone of violation*

Table 1. *The main laboratory parameters in the study groups, Me [Q25 %; Q75 %]*

Indicator	Group I (n=15)	Group II (n=13)	Group III (n=17)
1	2	3	4
Hemoglobin, g/l	127[121; 140]	128,9[110; 149]	132 [117; 138]
Erythrocytes, x10^{12}/l	4,34[3,2; 4,9]	4,25[3,03; 5,2]	4,52[3,9; 5,4]
Platelets, x10^{9}/л	231[134; 403]	174,5[98; 480]	210 [158; 390]
Leukocytes, x10^{9}/л	5,4[3,2; 8,7]	5,9[3,1; 10,6]	6,1 [3,9; 9,4]
Erythrocyte sedimentation rate, mm/h	27,2[7; 39]	30[5; 52]	26[14; 48]
General protein, g/l	67 [64; 78]	70 [63; 83]	72,4 [63; 82]
Albumin, g/l	40,6[36; 42]	39 [32; 43]	43,2 [34; 46]
AST, unit/l	69,2[34; 102]	82 [52; 206]	84,4[27; 74]
ALT, unit/l	113,2[49; 180]	83 [56; 265]	98[37; 159]
General bilirubin, μmol/l	14[9;28]	19 [5; 77]	16[12; 23]
Alkaline phosphatase, unit/l	158[114; 229]	381 [222; 1480]*	137[92; 280]
Gamma glutamyl transferase, unit/l	87,1[48; 145]	306 [183; 1157]*	71,2[54; 102]
Cholesterol, mmol/l	5,4[3,9; 6,8]	6,8 [4,7; 12,2]	6,9[4,3; 9,7]
Glucose, mmol/l	4,7[3,4; 5,7]	4,8 [3,3; 6,7]	5,9 [3,8; 7,4]
Circulating immune complexes, unit	72,1[55; 180]	177,4[75; 350]*	68 [44; 167]

Note: * p <0.05 when compared with group I and III.

deformity (54 %, n = 7), diffuse changes in pancreas (74 %, n = 11), indirect signs of portal hypertension (31 %, n = 4). EGDS revealed the signs of chronic gastritis or gastroduodenitis (70 %, n = 9), erosive gastritis (31 %, n = 4), cardia insufficiency (54 %, n = 7), esophageal varices (1.6 %, n = 2). One patient was diagnosed with chronic viral hepatitis C. When interpreting the results of an autoimmune liver panel, autoimmune origin of the disease was confirmed in 69.2 % (n = 9) of cases: increased titers of ANA (min. 1:640, max. 1:20,480) were detected; more often with a cytoplasmic type of luminescence, SMA (1:40), AMA (min. 1:320; max. 1:5,120). Morphological changes in liver biopsy samples were characterized by the presence of piecemeal (rarely — bridging) necrosis, portal tract infiltration with plasma cells, periductal lymphocytic infiltration, and periductal fibrosis. The degree of necroinflammatory response according to Knodell score was 6–9 points, liver fibrosis according to METAVIR was F 2–3.

During the analysis of clinical and laboratory data in group III (n = 17), attention was drawn to lipid metabolism disorders determined in 70.5 % (n = 12) of cases (Table 1). It should be mentioned that in 35.7 % (n = 5) of cases, impaired carbohydrate metabolism (increased fasting glucose level) was found, in contrast to groups I and II where blood glucose levels were within the reference values. Hepatitis virus markers were negative in all patients of this group. Liver autoimmune panel values were changed in two patients (11.7 %); they were characterized by increased ANA (1:320; 1:1,256) and AMA (1:160; 1:1,280).

According to ultrasound results, gallbladder pathology and signs of steatosis of the liver and pancreas were detected much more often in group III. Hepatomegaly was found in 52.9 % (n = 9) of cases, splenomegaly — in 35.2 % (n = 6), diffuse changes in liver parenchyma — in 35.2 % (n = 6), signs of liver steatosis — in 52.9 % (n = 9), thickening of gallbladder walls — in 70.6 % (n = 12), gallbladder deformation — in 41.2 % (n = 7), echo suspension in gallbladder — in 64.7 % (n = 11), diffuse changes in pancreas — in 47 % (n = 8), signs of pancreatic steatosis — in 35.2 % (n = 6), indirect signs of portal hypertension — in 17.6 % (n = 3).

According to EGDS results, there were signs of chronic gastritis or gastroduodenitis (70.6 %, n = 12), erosive gastritis (35.2 %, n = 6), cardia insufficiency (47 %, n = 8), esophageal varices (11.7 %, n = 2). The morphological presentation was characterized by fatty degeneration and inflammatory infiltration of sinusoids. In most cases, the degree of necroinflammatory reaction according to Knodell score was 4–5 points; liver fibrosis according to METAVIR was F 1–2.

To assess the reliability of signs, PHG data were compared to the results of the confirmation of patient condition (results of expert opinion obtained on the basis of total available data, excluding the PHG data). The correlation of sign values (positive or negative) with the results of the confirmation of patient condition is presented in Tables 2, 3 and 4. Specific aspects of intrahepatic blood flow disorders considering the level of localization of obstruction in the examined groups, are clearly described in Table 5.

Table 2. *Contingency table of the sign of viral hepatitis according to polyhepatography*

Polyhepatography result	Verification results*		Total
	VG not detected	VG not detected	
Impaired venous inflow	N= 11 (ИП)/ N= 11(TP)	N= 4 (ЛП)/ N= 4 (FP)	n=15
Other violations or absences	N= 1 (ЛО)/ N= 1 (FN)	N= 29 (ИО)/ N= 29 (TN)	n=30
Total	n=12	n=33	n=45

* Для верификации оценивались наличие или отсутствие маркеров вирусных гепатитов
Note: VG — viral hepatitis, TP — true positive, FP — false positive, TN — true negative, FN — false negative
* For verification, the presence or absence of markers of viral hepatitis was assessed

Table 3. *Contingency table of the sign of autoimmune liver disease according to polyhepatography*

Polyhepatography result	Verification results		Total
	AILD detected	AILD not detected	
Impaired arteriovenous inflow	N= 9 (ИП)/ N= 9 (TP)	N= 2 (ЛП)/ N= 2 (FP)	n=11
Other violations or absences	N= 5 (ЛО)/ N= 5 (FN)	N= 29 (ИО)/ N= 29 (TN)	n=34
Total	n=14	n=31	n=45

Note: AILD — autoimmune liver diseases

Table 4. Contingency table of the sign of steatohepatitis according to polyhepatography

Polyhepatography result	Verification results*		Total
	SG detected	SG not detected	
Impaired venous outflow	N= 14 (ИП)/ N= 14 (TP)	N= 6 (ЛП)/ N= 6 (FP)	n=20
Other violations or absences	N= 0 (ЛО)/ N= 0 (FN)	N= 25 (ИО)/ N= 25 (TN)	n=25
Total	n=14	n=31	n=45

Note: SG — steatohepatitis
* For verification of steatohepatitis, a set of indicators was taken, which included a set of data from clinical and biochemical blood tests, ultrasound of the abdominal organs, shear wave elastography of the liver with elastometry

Table 5. Characteristics of intrahepatic blood flow disorders among the examined patients, n (%)

PGG data (estimate Si)	Identified pathology (condition Ci)				ΣNSi
	C1	C2	C3	C4	
S1=VI	11 (24,4 %)	3 (6,7 %)	0	0	n=14
S2=AVI	1 (2,2 %)	9 (20 %)	0	1 (2,2 %)	n=11
S3=VO	0	2 (4,4 %)	14 (31,1 %)	4 (6,7 %)	n=20
ΣNCi	n=12	n=14	n=14	n=5	n=45

Note: VI — impaired venous inflow, AVI — impaired arteriovenous inflow, VO — disorders in the area of venous outflow, C1=viral hepatitis, C2=autoimmune liver diseases, C3=steatohepatitis, C4=liver pathology excluded

Based on the data obtained, sensitivity, specificity and accuracy of the proposed method of polyhepatography in the diagnosis of non-alcoholic steatohepatitis, viral and autoimmune liver diseases (AILDs) were determined. In cases of viral hepatic lesions, method sensitivity was 91.6 %, accuracy was 88.9 %, specificity was 87.8 %. When diagnosing AILDs, sensitivity was 64.2 %, method accuracy was 84.4 %, and specificity was 87.8 %. In non-alcoholic steatohepatitis, sensitivity was 100 %, accuracy was 86.7 %, specificity was 80.6 %.

Discussion

The main mechanism of intrahepatic blood flow disorders at the early stages of CLDs is a dynamic component determined by capillary vasoconstriction, activation of hepatic stellate cells (HSCs), decreased activity of nitric oxide (NO) and nitric oxide synthase (NOS). In patients with liver cirrhosis, this dynamic component amounts to 20–30 %. With the progression of a pathological process in liver, a significant place is taken by a mechanical component due to the development of fibrosis and inflammation [12]. Therefore, impaired portohepatic hemodynamics and CLDs progression has a close relationship that is recommended to use for the diagnosis of liver diseases. Our studies demonstrate that PHG as a technique for assessing intrahepatic blood flow is reasonable to be used as an instrument for the early diagnosis of liver diseases. The PHG technique has several advantages including non-invasiveness, easy conducting of examination, as well as the availability of the equipment required (a 4-channel rheograph with the ability to take a single-channel cardiogram and phonocardiogram is sufficient for examination according to PHG technique; rheographs of this type are the standard equipment of functional diagnostics room). PHG results are interpreted on the basis of the developed morphofunctional hemodynamic model that allows presenting complex intrahepatic hemodynamics in a simplified form. The developed algorithm for PGG data interpretation allows answering the clinically significant questions one by one: the presence of the signs of intrahepatic blood flow disorders, the level of localization of blood flow obstructions, the nature of disorders (persistent or functional), disease stage, changes in the state of liver during repeated examinations, personalized therapy selection and evaluation of its effectiveness. Considering the specificity of liver hemodynamic changes depending on the etiological factor, the data obtained can be additional diagnostic criteria in determining the etiology of liver diseases. If a patient has arteriovenous inflow disorders, it is highly likely that autoimmune hepatitis can be assumed; if a patient has venous inflow disorders, then it can be viral hepatitis; and if a patient has venous outflow disorders, it can be steatohepatitis. The analysis of the results obtained is in good agreement with known and generally accepted ideas about intrahepatic hemodynamics and morphofunctional hemodynamic model. Curves of the integral rheography of the body and of the rheography of

pulmonary artery demonstrate the initial conditions of systemic blood circulation — the pump function of left ventricle and the diastolic function of right ventricle. Correspondence of these curves to the conditional normal range is an important condition for the correct interpretation of rheograms in the area of the liver and spleen. If a patient has central hemodynamics disorders, the assessment of rheograms should be carried out considering the identified changes in central hemodynamics [13].

At the same time, despite the fact that PHG has critical advantages (non-invasiveness, a simple examination protocol, and the availability of the equipment required), the main difficulty for the widespread implementation of the PHG technique into clinical practice is the reliable interpretation of the obtained PHG data. However, at present this is not an insurmountable obstacle, since modern mathematical methods and software tools that implement them are widely used both for the primary analysis of instrumental data (for example, for automatic labeling of cardiograms and their primary analysis), and as a means of assisting in the interpretation of the results of instrumental examinations in particular, machine learning algorithms are used to define the possible presence and location of malignant neoplasms according to x-ray examinations). Using the capabilities of advanced computational methods significantly increases the availability of various diagnostic techniques and reduces the risk of errors. The use of this approach for the analysis of PHG data obtained will provide free access for patients to a simple instrument for early non-invasive diagnosis of liver diseases and subsequent follow-up of patients regardless of their proximity to the center of competence [4].

A current option for implementing this idea is the development of a telemedicine service that is a center of competence according to the PHG technique, accumulates the algorithm for training and retraining the predictive model, the training set, the trained model itself and provides services for the remote interpretation of study data. This scheme for the provision of services for the remote interpretation of instrumental examinations is currently already implemented in Russia. It should be mentioned that, according to the Accounts Chamber, the number of requests for remote description and interpretation of instrumental examination data is more than 96 % of the total number of requests for telemedicine consultations in 2017–2018 (among them — interpretation of electrocardiographic examinations (A05.10.004.001) — 81.4 %, description and interpretation of X-ray results (A06.30.002.004) — 15.4 %) [4]. Thus, the development of PHG in this direction is considered to be extremely promising.

Conclusion

1. Polyhepatography is a non-invasive technique for the integral assessment of intrahepatic microcirculation that is characterized by high sensitivity, sufficient specificity, and diagnostic accuracy.

2. Considering the specificity of liver hemodynamic changes depending on the etiological factor and the stage of the disease, polyhepatography can be used as a screening method for examining patients.

3. Changes in intrahepatic blood flow found during PHG can be additional diagnostic criteria in determining the etiology of liver diseases and control of changes over time during etiopathogenetic therapy.

Вклад авторов:

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ДИАГНОСТИКА И КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ «СКРЫТЫХ» СПЕКТРАЛЬНЫХ НАРУШЕНИЙ ОКСИГЕНАЦИИ КРОВИ У КУРИЛЬЩИКОВ С ОБОСТРЕНИЕМ БРОНХИАЛЬНОЙ АСТМЫ

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Diagnosis and Clinical Significance of «Hidden» Spectral Disorders of Blood Oxygenation Among Smokers with Exacerbation of Bronchial Asthma

Резюме

Цель — выявить и оценить клиническое значение «скрытых» нарушений оксигенации крови у курильщиков с обострением бронхиальной астмы. **Материалы и методы.** Обследовано 19 курильщиков(средний возраст 54,6±2,05 лет) с обострением смешанной (68 %) или аллергической (32 %) бронхиальной астмы. Пациентам проводились: спирометрия, пульсоксиметрия, СО-метрия выдыхаемого воздуха. **Результаты:** точность клинической оценки оксигенации крови у курильщиков с обострением бронхиальной астмы существенно возросла после коррекции уровня оксигемоглобина (SpO_2) на карбоксигемоглобин (HbCO)с помощью разработанной оригинальной программы ЭВМ, что позволило у пациентов с бронхиальной астмой своевременно диагностировать жизнеугрожающее обострение данного заболевания за счёт выявления «скрытой» дыхательной недостаточности.

Ключевые слова: *табакокурение, «скрытые» спектральные нарушения оксигенации крови, дыхательная недостаточность*

Конфликт интересов

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

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Abstract

The purpose of the study — to identify and evaluate the clinical significance of "hidden" disorders of blood oxygenation in smokers with exacerbation of bronchial asthma. **Materials and methods:** spirometry, pulse oximetry, CO-metry of exhaled air. To diagnose "hidden" disorders of blood oxygenation, including "hidden" violations of the spectral characteristics of the level of hemoglobin oxygen saturation, 19 male smokers (middle age 54,6±2,05 years) with exacerbation of mixed (68 %) or allergic (32 %) bronchial asthma were examined. **The results:** the accuracy of the clinical assessment of blood oxygenation in smokers increased significantly after the correction of the SpO_2 level to the level of carboxyhemoglobin with the help of a computer program developed by us, which made it possible to diagnose a clinically significant life-threatening exacerbation of this disease in smoking patients with bronchial asthma, since "hidden" respiratory insufficiency was detected in a timely manner.

Key words: *tobacco smoking, «hidden» violations of the spectral characteristics of the level of hemoglobin oxygen saturation, respiratory failure*

Conflict of interests

The authors declare no conflict of interests

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BA — bronchial asthma, CO — carbon monoxide, HbCO — carboxyhemoglobin, O_2 — oxygen, PY — pack-year, SpO_2 — transcutaneous level of hemoglobin saturation with oxygen

Introduction

Tobacco smoking is one of the known exogenous sources of carbon monoxide (CO) in human body. Carbon monoxide displaces oxygen (O_2) with the formation of carboxyhemoglobin (HbCO) that results in various impairments of the oxygen transport function of blood, therefore, it is necessary to define HbCO level in smokers, especially if they have chronic bronchial and obstructive pathology [1–3]. This diagnostic approach allows clarifying and objectifying the assessment of blood oxygenation disorders, in particular, in smokers with bronchial asthma (BA).

The prevalence of smoking in patients with bronchial asthma is high. It was established that 25–35 % of patients with bronchial asthma are active smokers [4, 5]. Tobacco smoke in some smokers with asthma leads to the neutrophilic transformation of airway inflammation with more frequent and more severe exacerbations of bronchial asthma [6, 7].

Transcutaneous two-wavelengths pulse oximetry is most widely used worldwide to assess blood oxygenation, however, it leads to a diagnostic error in smokers, since carboxyhemoglobin absorbs infrared light almost identically to oxyhemoglobin. As a result, the level of the oxygen saturation of hemoglobin in smokers according to transcutaneous two-wavelengths pulse oximetry is always overestimated [8–12].

The advanced two-wavelengths pulse oximeters allow monitoring blood oxygenation and conducting its spectral analysis to determine the percentage of blood oxygen saturation (SpO_2) in the ranges of 95–100 %, < 95 %, 90–94 %, 85–89 %, etc. [13]. However, the levels, as well as the spectral characteristics of hemoglobin oxygen saturation, without considering carboxyhemoglobin are always aberrant. The clinical significance of this aberration is confirmed by the data from the federal guidelines Carbon Monoxide Poisoning; they confirm that the level of HbCO in non-smokers is 1–2 %, whereas in smokers it ranges from 5 to 10 %, with average daily concentration of HbCO from 5 up to 15 % [14].

The reliable information about the exact level and spectral characteristics of SpO_2 is crucial for diagnosis and assessment of the severity of respiratory failure, in particular, in life-threatening asthma exacerbation. One of the most important diagnostic criteria for a life-threatening BA exacerbation is the blood oxygenation decrease below 92 %.

The objective of this study was to identify and to evaluate the clinical significance of the "occult" blood oxygenation impairments in smokers with asthma exacerbation.

Materials and Methods

For the diagnosis of the "occult" impairments of blood oxygenation, including "occult" impairments of the spectral characteristics of SpO_2, 19 male smokers aged (54.60 ± 2.05), with exacerbation of mixed (n = 13; 68 %) or allergic (n = 6; 32 %) asthma were examined. It was a cross-sectional study; informed consent

Table 1. *Clinical characteristics of smokers with bronchial asthma*

Signs	Smokers with bronchial asthma, n=19
Age, years	52,2±2,69
Men, %	100
Tobacco smoking, %	100
Disease duration, years	27,9±1,45
Duration of tobacco smoking, years	26,5±2,37
Mixed bronchial asthma, %	68
Allergic bronchial asthma, %	32
Allergens, %	100
Viral infection, %	15
Urticaria, %	7,3
Eosinophilia of blood and/or sputum, %	11
Arterial hypertension, %	17
Obesity, %	27
Angina pectoris II-III functional class, %	27
Type II diabetes mellitus with a target blood sugar level, %	14

was obtained. BA was diagnosed in accordance with the Clinical Guidelines for Asthma-2021 of the Ministry of Health of the Russian Federation [7]. Table 1 presents clinical characteristics of patients.

In all patients, carboxyhemoglobin level was analyzed using a Micro CO-monitor (Micro Medical, UK) by the carbon monoxide fraction in the exhaled air. HbCO was measured no earlier than 2 hours after smoking.

M. J. Jarvis et al. conducted a study to evaluate the accuracy of exhaled air CO measurement in comparison with gas chromatography results. The results obtained confirmed the high accuracy of HbCO evaluation by FECO measurement — the correlation coefficient in assessing the accuracy of HbCO measurement by these methods was 0.98 for "healthy" smokers and 0.92 for smoking patients with emphysema [1].

Ventilatory lung capacity was assessed using a Spirodoc SpO_2 spirometer (Italy).

Blood oxygenation was assessed using a 15-minute transcutaneous two-wavelength pulse oximetry at rest using a Spirodoc SpO_2 spirometer (Italy). The analysis of hemoglobin oxygen saturation, including spectral characteristics of SpO_2, was performed both without and with regard of carboxyhemoglobin. To adjust the results of monitoring blood oxygenation for HbCO, we used our proprietary Software for Carboxyhemoglobin Adjustment of Blood Oxygenation Monitoring Results During Transcutaneous Two-Wave Pulse Oximetry (https://elibrary.ru/item.asp?id=43888052&ysclid=l7ulwur86q612655985).

Software language and user interface are implemented in Java Script language using HTML and CSS. The software is provided as source code under the terms of the GNU General Public License. Implementing computer types — Intel, ARM, MIPS, operating system versions — Windows, Linux, FreeBSD.

Algorithm for using the software

1. Monitoring of blood oxygenation using transcutaneous two-wavelength pulse oximetry.
2. Extraction of the blood oxygenation dataset from the SpO_2 curve recorded by Spirodoc SpO_2 and its loading into the software.
3. Adjustment of blood oxygenation data for HbCO average level after the introduction of average HbCO value in the software.

Statistical processing of study results was carried out using a licensed Russian version of Statistica 13.3 software. Mann — Whitney U test was used to compare the parameters. The results are presented as (M ± m). The differences in the analyzed values were considered to be statistically significant at the level of α-error < 0.05.

Results and Discussion

A moderate BA exacerbation was observed in 5 patients (26 %), a severe exacerbation — in 8 patients (42 %), and a life-threatening exacerbation — in 6 patients (32 %) according to the level of peak expiratory flow and clinical signs of the severity of BA exacerbations. However, none of the examined patients demonstrated clinically significant decreased SpO_2 below 92 % (as measured by pulse oximetry with no subsequent adjustment for carboxyhemoglobin).

The main clinical signs of bronchial and obstructive pathology in smokers were: paroxysmal cough in 5 (27 %) individuals, episodes of labored breathing in 19 (100 %) individuals, shortness of breath at heavy physical activity in 7 (39 %) individuals, at moderate physical activity — in 10 (51 %) individuals, and shortness of breath at rest — in 2 (10 %) patients. Predominantly mucous sputum was observed in 4 (19 %) patients. All patients underwent chest X-ray to exclude pneumonia.

According to the pack-year (PY) parameter, 5 patients with asthma were identified as "absolute smokers" (PY > 10, 26 %) and in 10 — as "heavy smokers" (PY > 25, 53 %). In 4 patients (21 % of cases), smoking was less intense and less prolonged (PY ≤ 10). Mean carboxyhemoglobin level exceeded the upper limit of normal (< 1.12 %) and amounted to (2.40 ± 0.17)%. The pack-year parameter was at the level of (35.10 ± 5.15) due to the predominance of the "heavy" smokers category. The average duration of hospital stay was (11.10 ± 0.40) days.

Table 2. *Characteristics of lung ventilation in smokers with bronchial asthma*

Indicators, (M±m)	Smokers with bronchial asthma, n=19
VC, %	54,7±3,97
FVC, %	42,3±3,33
FEV_1, %	40,0±3,56
FEV_1/ VC, %	58,5±5,38
FEV_1/ FVC, %	67,9±4,11
COC_{25-75}, % MEF_{25-75}, %	32,5±4,33

Note: VC — vital capacity of the lungs; FVC — forced vital capacity of the lungs; FEV_1 — volume of forced exhalation in 1 sec.; MEF_{25-75} –middle expiratory flow of 25-75 % FVC

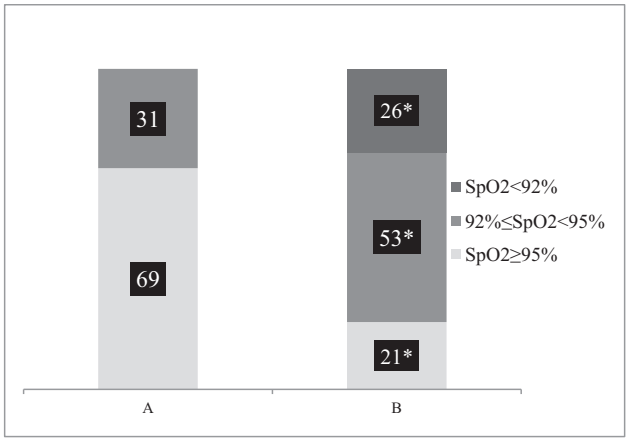

Figure 1. *Prevalence of normal (SpO2≥95 %), moderately reduced (92 %≤SpO2<95 %) and clinically significant reduced (SpO2<92 %) blood oxygenation without correction (A) and with correction for carboxyhemoglobin (B)*

Note: * — probability of α-error <0,05 when comparing indicators

All examined patients were found to have an obstructive respiratory dysfunction, with a decreased lung vital capacity (VC) and forced vital capacity (FVC), as well as the ratio of forced expiratory volume per 1 second (FEV_1) to VC (FEV_1/VC) and FVC (FEV_1/FVC), see Table 2. It is known that VC decreases in severe obstruction, and air-trapping that develops both during smoking and BA exacerbation contributes to a decrease in FVC.

When performing pulse oximetry without subsequent adjustment of the mean value of hemoglobin saturation with oxygen for carboxyhemoglobin, the saturation of hemoglobin with oxygen in all examined patients exceeded 92 %. It is worth mentioning, that normal mean SpO_2 values (SpO_2mean ≥ 95 %) were found in 13 (69 %), and moderately reduced mean values (92 % ≤ SpO_2mean < 95 %) — in 6 (31 %) smokers with asthma exacerbation.

Adjustment of hemoglobin oxygen saturation for HbCO (the mean value of carbon monoxide in the exhaled air used to determine carboxyhemoglobin level is presented in Table 3 below) allowed identifying "occult" impairments of blood oxygenation in 9 (48 %) patients. The prevalence of normal mean oxygenation values decreased from 69 to 21 %, and the prevalence of moderately decreased mean hemoglobin oxygen saturation increased from 31 to 53 %. Five (26 %) smokers demonstrated a decrease in SpO_2 below 92 %; it is typical for a life-threatening BA exacerbation (Figure 1).

As a result, the concept of BA exacerbation severity in the examined smokers with asthma has fundamentally changed: the prevalence of moderate exacerbation decreased from 26 (n = 5) to 21 % (n = 4), of severe — from 42 (n = 8) to 26 % (n = 5), and the prevalence of life-threatening exacerbation increased from 32 (n = 6) up to 53 % (n = 10) — p < 0.05 (Figure 2).

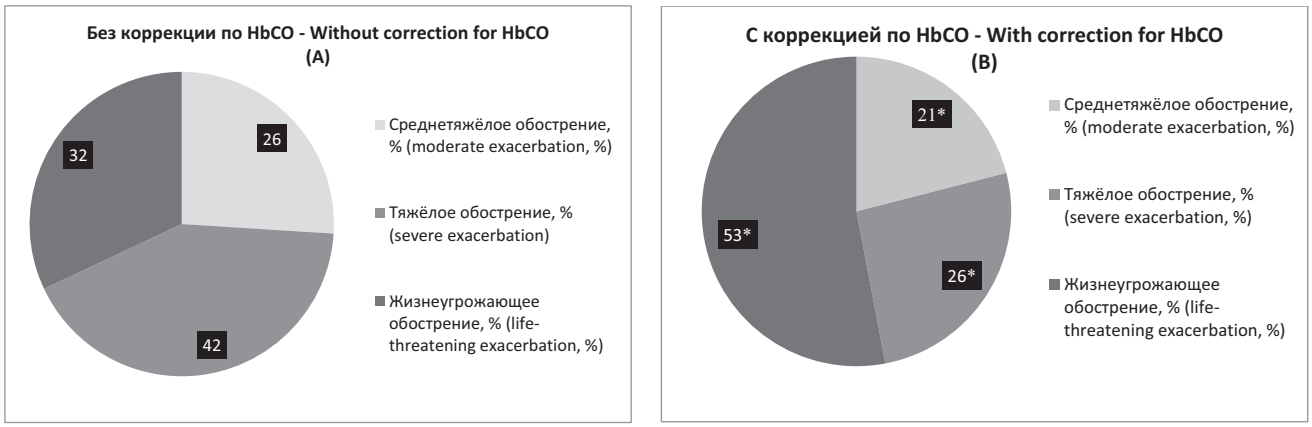

Figure 2. *Prevalence of severity of bronchial asthma exacerbation among smokers depending on the correction for carboxyhemoglobin*

Note. A — without correction for HbCO; B — with correction for HbCO; * — probability of α-error < 0.05 when comparing the parameters

Table 3. *Assessment of blood oxygenation in smokers with bronchial asthma with and without correction for carboxyhemoglobin*

Parameters	Without correction for HbCO, (M ± m)	With correction for HbCO, (M ± m)	p
F_ECO, ppm	-	15.60 ± 0.09	-
HbCO, %	-	2.40 ± 0.17	-
SpO_2min., %	93.80 ± 0.34	91.40 ± 0.39	< 0.001
SpO_2max., %	97.10 ± 0.24	94.60 ± 0.31	< 0.001
SpO_2mean, %	95.60 ± 0.29	93.20 ± 0.33	< 0.001
SpO_2 (< 95 %), %	20.70 ± 7.30	80.80 ± 8.53	< 0.001
SpO_2 (< 92 %), %	-	24.90 ± 7.82	-
SpO_2 (< 90 %), %	-	1.60 ± 0.75	-
SpO_2 (95–100 %), %	79.30 ± 7.30	19.20 ± 8.53	< 0.001
SpO_2 (95–100 %)mean, %	96.00 ± 0.20	95.50 ± 0.10	0.196
SpO_2 (90–95 %), %	20.70 ± 7.30	79.30 ± 8.37	< 0.001
SpO_2 (90–95 %)mean, %	93.80 ± 0.06	93.00 ± 0.24	0.022
SpO_2 (85–90 %), %	-	1.50 ± 0.75	-
SpO_2 (85–90 %)mean, %	-	89.50 ± 0.20	-

Note. F_ECO — fraction of carbon monoxide in exhaled air; HbCO — carboxyhemoglobin; SpO_2min., max., mean — minimum, maximum and average values of SpO_2; SpO_2(< 95 %) SpO_2 (< 92 %) SpO_2 (< 90 %), SpO_2 (95–100 %), SpO_2 (90–95 %), (85–90 %) — part of SpO_2 values related to the specified oxygenation spectra; SpO_2 (95–100 %)mean, SpO_2 (90–95 %)mean, SpO_2 (85–90 %)mean — the average level of SpO_2 in the indicated blood oxygenation spectra; p — the probability of α-error < 0.05 when comparing corrected and uncorrected for HbCO parameters of blood oxygenation

It is apparent that the accuracy of the clinical assessment of blood oxygenation in smokers after adjusting SpO_2 for HbCO level increased significantly and allowed diagnosing a clinically significant life-threatening exacerbation of asthma in smoking patients due to the timely detection of respiratory failure.

In addition to decreased mean, minimum and maximum SpO_2, adjustment of blood oxygenation monitoring data for HbCO allowed revealing significant changes in the basic spectra of blood oxygenation (Table 3).

In particular, the part of the normal values of blood oxygenation (95–100 %) decreased from 79.3 to 19.2 %. It should be noted that, for example, the proportion of decreased SpO_2 values (90–95 %) increased significantly from 20.7 to 79.3 % in combination with a decrease in the mean values of blood oxygenation in the indicated blood oxygenation spectra.

Conclusion

The negative effect of carbon monoxide on the oxygen transport function of blood is implemented due to hypoxic hypoxia (due to decreased partial pressure of O_2 in alveolar space), hemic hypoxia (due to excessive carboxyhemoglobin, HbCO), circulatory hypoxia (due to hemodynamic disorders), and tissue hypoxia (due to inactivation of enzymes that regulate tissue respiration). Further, the increase in HbCO level shifts the oxyhemoglobin dissociation curve to the left with a decrease in the rate of oxygen delivery to tissues. The higher HbCO, the more impaired the state of oxygen transport in a smoker is.

Due to elevated HbCO levels in all smokers, transcutaneous pulse oximetry is subject to diagnostic error due to similar absorption of infrared light by HbO_2 and HbCO; it leads to an "underestimation" of blood oxygenation disorders and, accordingly, to an "underestimation" of the severity of respiratory failure that occurs in some patients with chronic bronchial and obstructive pathology.

Therefore, timely detection and more accurate diagnosis of respiratory failure required adjustment for carboxyhemoglobin level after two-wavelength transcutaneous pulse oximetry. This determines the practical significance of this study. For practical adjustment of SpO_2 monitoring results we can use, for example, a computer program developed by us.

This diagnostic strategy is also important for the subsequent treatment the nature and extent of which largely depend on timely and more accurate assessment of respiratory failure.

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

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