ISSN 2409-9988

Inter Collegas

Experientia docet

2024

11(4)

INTER COLLEGAS

2024
Vol. 11 No.4

OFFICIAL JOURNAL OF KHARKIV NATIONAL MEDICAL UNIVERSITY
ISSN 2409-9988

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Periodicity:
4 times a year

Indexing and archiving:
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National accreditation (Ukraine):
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INTER COLLEGAS. 2024. VOL. 11, No.4
ISSN 2409-9988

Content

https://doi.org/10.35339/ic.11.4

THERAPY

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EPIDEMIOLOGY & PUBLIC HEALTH

EFFICIENT USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR TREATMENT OF JOINT PAIN IN THE PRACTICE OF PHYSICIANS AND PHARMACISTS

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https://doi.org/10.35339/ic.11.4.mmr

ABSTRACT

Background. Due to the prevalence of dystrophic degenerative diseases, the annual increase in the number of visits from young and middle-aged patients leading an active lifestyle, and the growing frequency of traumatic injuries of various origins, the problem of joint pain is particularly relevant.

Aim. To investigate the main factors influencing the effective and safe use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in the treatment of joint pain syndrome.

Materials & Methods. Using the developed questionnaire, patients with articular pain syndrome were interviewed about the safety and rational use of NSAIDs.

Results & Conclusions. It was found that most often, people of working age with moderate intensity of pain syndrome sought medical care for joint pain. In one third of respondents, pain was accompanied by impaired motor activity in the joint. The largest proportion of respondents used oral systemic NSAIDs to reduce pain (46.7%), mainly non-selective cyclooxygenase inhibitors. A small proportion of patients (13.3%) who used NSAIDs topically preferred diclofenac, ibuprofen, and ketoprofen in the form of ointments and gels. 16.7% of respondents increased the dose of the drug on their own to achieve the desired therapeutic effect. 26.7% of patients simultaneously used several drugs from the NSAID group. However, the majority of the surveyed patients (63.3%) were not informed about the possibility of side effects associated with these drugs. A wide range of modern NSAIDs, a variety of dosage forms, high frequency and duration of use, and the potential risk of side effects require individual prescribing of drugs in this group. Prescribing timely and adequate treatment with a fast, effective and safe pain reliever remains an urgent issue in the daily practice of physicians and pharmacists.

Keywords: *dosage form, side effects, gastropathy, selectivity*.

Introduction

Arthralgia (joint pain) is a symptom that occurs in the joint area and can be the result of pathological processes in the joint itself, as well as in the structures surrounding it. Current data on the prevalence of chronic diseases indicate that the pathology of the musculoskeletal system has become one of the main causes of disability, especially among people aged 40–65 and over 65 [1]. Due to the prevalence of dystrophic degenerative diseases, the annual increase in the number of visits among people aged 40–65 and over 65 [1]. Due to the prevalence of dystrophic degenerative diseases, the annual increase in the number of visits from young and middle-aged patients leading an active life, and the growing frequency of traumatic injuries of various origins, the problem of joint pain is particularly relevant. According to statistics, NonSteroidal Anti-Inflammatory Drugs (NSAIDs) are the most commonly used medicines by healthcare professionals and the general public to treat joint pain and are the world's leading drugs in terms of consumption [2]. The use of NSAIDs leads to a decrease in pain, signs of local inflammation and fever. The responsible specialist should have a good command of the principles of rational prescription of NSAIDs for patients with joint pain syndrome to ensure effective pharmacotherapy and reasonable use of NSAIDs, select

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the most optimal drug with the best tolerability for a particular patient based on knowledge of clinical pharmacology.

The **aim** of a study was the identification and analysis of the main factors influencing the effective and safe use of NSAIDs in the treatment of joint pain syndrome.

Material & Methods

To achieve the aim of the study, 60 patients with articular pain syndrome were surveyed regarding the safety and rational use of NSAIDs, including sociodemographic, general clinical data and pharmacotherapeutic analysis. The pain syndrome was assessed using a Visual Analog Scale (VAS). In all patients, data on the pharmacotherapy received (type of NSAIDs, method of drug selection and features of use, duration of administration, clinical efficacy and side effects, use of additional drugs) were systematized. The study results were processed using a statistical Microsoft Excel software package. Continuous variables were expressed as mean ± standard deviations, as well as the percentage frequency of the phenomenon were calculated.

Results & Discussion

The average age of the surveyed patients with arthralgia was (49.47±2.60) years. According to the level of education, the surveyed patients were distributed as follows: 26.7 % with higher education, 10.0% with specialized secondary education, and 63.3% with secondary education. Overweight was diagnosed in 30.0% of respondents. The number of patients (57.0%) who reported doing enough daily physical activity was slightly higher than the number of those who were sedentary. The vast majority of respondents (70.0%) reported pain associated with changes in the knee joints, which, along with the hip joints, are among the supporting joints and carry a significant load. Restriction of motor activity in the joints was noted by 37.0% of the respondents. When analyzing the patients' condition according to the VAS scale, the severity of pain syndrome averaged (5.18±0.32) points, which corresponded to moderate pain.

It is known that the basis for a responsible approach to self-medication is the availability of complete information about the drug. When choosing a drug from the NSAIDs group, patients were equally guided by doctor's recommendations and advice from relatives and friends (43.3% each). For 13.3% of respondents, a pharmacist was the source of information about the medicines.

The largest proportion of respondents (46.7%) used tablet forms of medications to reduce joint pain (most respondents used non-selective CycloOXygenase (COX) inhibitors "traditional" NSAIDs: diclofenac, ibuprofen, paracetamol, naproxen, metamizole). 13.3 % of respondents preferred topical medications. The combined use of oral NSAIDs and topical agents was observed in 20.0% of cases, and the addition of a parenteral agent to this combination was observed in 13.3% of patients, respectively. Injectable forms of drugs in combination with topical medications were used to relieve arthralgia in 6.7% of patients. The analysis of the data showed that the vast majority of respondents (76.7%) reported significant efficacy from taking the prescribed NSAIDs. However, 23.3% of patients noted that the prescribed medication helped only partially. It should be noted that a small proportion of patients (16.7%) increased the dose of the drug on their own to achieve the desired therapeutic effect. The majority of respondents (73.3%) adhered to the prescribed treatment regimen. However, 26.7% of patients simultaneously used several drugs from the NSAID group, which is one of the risk factors for side effects from this group of drugs [3–5]. Combination drugs were preferred by 30.0% of respondents.

The most frequent and dangerous Adverse Events (AEs) with systemic use of NSAIDs include gastrointestinal complications, including symptoms of dyspepsia, erosion, and ulcers. Topical agents can cause redness at the site of application, itching, rashes, burning, and dry skin. However, most of the surveyed patients (63.3%) were not informed about the possibility of these side effects. According to the literature, patients with joint syndrome often have a significant number of comorbidities [6]. Concomitant hypertension, arrhythmia, peptic ulcer disease, and gastritis were detected in 63.3% of respondents. At a certain stage of the pain syndrome course, exacerbation of comorbidities can combine and complicate the management of patients with pain syndrome. Conversely, the presence of chronic pain syndrome may be an additional risk factor for premature death among older patients with comorbidities. It should be noted that patients with concomitant gastrointestinal disorders used NSAIDs while taking proton pump inhibitors on the recommendation of a physician or pharmacist. It is known that risk factors for NSAID gastropathy include concomitant use of glucocorticoids or anticoagulants/antiplatelet agents. Among the surveyed patients, 12 patients received clopidogrel and 7 patients received a glucocorticosteroid in combina-

tion with systemic and topical NSAIDs. The choice of NSAIDs for therapy must necessarily be made taking into account these factors, since concomitant use of glucocorticosteroids doubles the risk of gastrointestinal complications, and anticoagulants and antiplatelet agents increase the risk of bleeding [3; 7].

After analyzing the data obtained, it was found that most often people of working age seek medical care for joint pain, which emphasizes not only the medical but also the social importance of the problem of treatment, with moderate pain syndrome. The identified factors (one-third of patients are overweight, most patients do not follow a diet, and almost half of the surveyed individuals do not have sufficient daily physical activity) are associated with the onset of pain syndrome. The largest proportion of respondents used oral systemic NSAIDs to reduce pain, mostly non-selective COX inhibitors. According to international clinical guidelines, topical NSAIDs are currently recommended by the American Association of Orthopaedic Surgery (AAOS), National Institute for Clinical Excellence (NICE), International Society for Osteoarthritis Research (OARSI) as first-line therapy, in particular in the treatment of joint pain in osteoarthritis [8; 9]. In the updated ACR guidelines, the use of topical NSAIDs is indicated instead of oral medications, especially in patients over 75 years of age. According to the Cochrane analysis [1; 10; 11], diclofenac, ibuprofen and ketoprofen were found to be the most effective for the treatment of acute musculoskeletal pain among the 16 analyzed NSAIDs when applied transdermally. It should be noted that the small proportion of surveyed patients (13.3%) who used NSAIDs topically chose these medications in the form of ointments and gels. It was found that patients who were not satisfied with the analgesic effect achieved began to increase the dose or add other NSAIDs on their own, which only increases the risk of side effects but does not enhance the analgesic effect.

Conclusions

The wide range of modern NSAIDs, the variety of dosage forms, the high frequency and duration of use of these drugs, and the potential risk of side effects require individualized prescribing of drugs in this group. Given the above, prescribing timely and adequate treatment with a fast, effective and safe pain reliever remains an urgent issue in the daily practice of physicians and pharmacists.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

Funding Sources

There are no external sources of funding.

Consent for publication

All authors give their consent to publication.

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Received: 31 Oct 2024
Accepted: 31 Dec 2024

Cite in Vancouver style as: Meretskyi VM, Meretska IV, Redko SV. Efficient use of non-steroidal anti-inflammatory drugs for treatment of joint pain in the practice of physicians and pharmacists. Inter Collegas. 2024;11(4):5-8. https://doi.org/10.35339/ic.11.4.mmr

Archived: https://doi.org/10.5281/zenodo.14756968

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EVALUATING LIVER FIBROSIS: THE ROLE OF ELASTOGRAPHY AND FIBROTEST IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND INSULIN RESISTANCE

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https://doi.org/10.35339/ic.11.4.koz

ABSTRACT

Background. Non-Alcoholic Fatty Liver Disease (NAFLD), a common chronic liver disease, is often associated with Insulin Resistance (IR), which accelerates fibrosis progression. As NAFLD prevalence rises, understanding IR's role in liver damage is crucial. Non-invasive methods like elastography and FibroTest help assess fibrosis severity but remain underexplored in NAFLD patients with IR.

Aim. To compare liver elastography and FibroTest results in patients with isolated non-alcoholic fatty liver disease and NAFLD with insulin resistance, assessing fibrosis differences and the effect of comorbidity on disease progression.

Materials and Methods. NAFLD patients were divided into two groups: isolated NAFLD, and NAFLD with IR. Liver stiffness was measured via elastography, fibrosis levels via FibroTest, and laboratory markers (including Alanine aminoTransferase (ALT), Aspartate aminoTransferase (AST), protein metabolism) were analyzed to evaluate liver function

Results. Patients with NAFLD and IR had significantly higher elastography values (10.5 kPa vs. 6.2 kPa in isolated NAFLD). ALT and AST levels were elevated in the IR group (ALT 65 U/L, AST 59 U/L), while protein metabolism indicators were lower, reflecting greater liver dysfunction. Strong correlations were found between elastography and ALT (r=0.844) and AST (r=0.822). FibroTest scores were higher in the IR group (0.78 vs. 0.58 in isolated NAFLD), indicating more advanced fibrosis.

Conclusions. IR accelerates fibrosis in NAFLD, with elastography and FibroTest effectively differentiating fibrosis severity. These findings support their use in clinical practice for improved assessment and management, particularly in NAFLD patients with IR. Further research is needed to refine treatment strategies.

Keywords: *steatosis, metabolic syndrome, sheer-wave elastography, MAFLD.*

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD), also known as metabolic-associated steatotic liver disease [1] or simply steatotic liver disease, is rapidly emerging as one of the most prevalent chronic liver conditions worldwide. Affecting millions of individuals, it represents a significant public health concern [2]. The global rise in NAFLD prevalence has been driven in part by increasing rates of obesity and metabolic syndrome, situating NAFLD as a leading contributor to liver-related morbidity and mortality. According to recent epidemiological studies, the global prevalence of NAFLD ranges from 25% to 45% in the general population, with even higher rates observed in individuals with obesity or type 2 diabetes [3; 4]. This alarming trend underscores the urgent need for effective prevention and management strategies.

Concurrently, Insulin Resistance (IR) has reached pandemic proportions, increasingly recognized as a central feature of metabolic dysfunction and a key risk factor for cardiovascular and endocrine diseases [5]. It is estimated that up to 75% of individuals with NAFLD exhibit varying degrees of IR [6]. The relationship between IR and NAFLD is complex, as IR not only contributes to

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the development of hepatic steatosis but also influences the progression of liver injury, inflammation, and fibrosis. While IR has been implicated in the progression of NAFLD, its precise impact on liver disease severity and fibrosis progression remains insufficiently studied, particularly regarding its comorbid presentation with NAFLD. Research indicates that IR is associated with a higher likelihood of advanced fibrosis in NAFLD patients. However, the mechanisms through which IR exacerbates liver damage, including alterations in lipid metabolism and inflammatory responses, require further investigation.

Elastography has become the gold standard in non-invasively assessing liver health and quantifying fibrosis levels, offering clinicians critical insights into disease stage and prognosis. Studies have demonstrated that elastography correlates well with histological findings of liver fibrosis, making it a reliable tool for monitoring disease progression and treatment response [7]. Additionally, the FibroTest, a non-invasive biomarker-based tool, provides an alternative method for evaluating liver fibrosis and its stages, utilizing a combination of clinical and laboratory data to enhance diagnostic accuracy [8]. The FibroTest is particularly advantageous in clinical settings where liver biopsy is not feasible, allowing for regular monitoring of liver health.

Despite the widespread utility of both elastography and FibroTest, there remains a knowledge gap regarding the combined impact of IR and NAFLD on liver fibrosis and overall hepatic status. Current literature suggests that patients with NAFLD and IR exhibit significantly higher levels of liver stiffness, indicative of increased fibrosis. Exploring the effects of IR on NAFLD progression, including fibrosis severity and disease advancement, is essential to improve patient management and outcomes for those presenting with both conditions. Furthermore, understanding this relationship could inform targeted therapeutic approaches aimed at mitigating the detrimental effects of IR on liver health.

Aim. To conduct a comparative analysis of liver elastography indicators and fibrotest in patients with isolated NAFLD and in patients with NAFLD complicated by insulin resistance, in order to identify differences in fibrosis levels and evaluate the impact of comorbidity on disease progression.

Materials and Methods

To achieve the stated aim, 137 patients were examined, consisting of 86 men and 51 women aged between 18 and 70 years. All patients underwent assessments to exclude comorbid conditions and complications that could affect the validity of the study results. Exclusion criteria included the presence of viral hepatitis (associated with Hepatitis B, C and D virus infections), liver cirrhosis, alcohol abuse (defined as consumption above the physician-recommended limits of >30 g of ethanol/day for men and >20 g of ethanol/day for women, or other alcoholic beverages converted to ethanol equivalents), toxic and drug-induced liver diseases, autoimmune liver diseases, the use of medications that could lead to cytolytic, mesenchymal-inflammatory, or cholestatic syndromes, and chronic diseases in a state of decompensation or exacerbation, including type 1 or type 2 diabetes mellitus.

Inclusion criteria were met by patients with confirmed diagnoses of NAFLD and insulin resistance (evidenced by elevated insulin levels and the calculation of the HOMA-IR index (Homeostatic Model Assessment of Insulin Resistance), a widely used method for assessing insulin resistance based on fasting glucose and insulin levels. It is calculated using the formula:

$$\text{HOMA-IR index} = \text{insulin } (\mu U/mL) \times \text{glucose } (mmol/L) / 22.5 \quad (1)$$

A HOMA-IR index value below 2.0–2.5 is generally considered normal, while elevated HOMA-IR index indicates insulin resistance, which is commonly associated with metabolic syndrome, NAFLD, and type 2 diabetes. This method is useful for screening and evaluating metabolic disturbances but should be interpreted alongside other clinical and laboratory findings.

Following the initial assessment, all patients were divided into two groups: Group 1 consisted of patients with comorbid NAFLD and IR (n=76), while Group 2 included patients with isolated NAFLD (n=61). Both groups were comparable in terms of patient numbers, age distribution, and gender.

All patients underwent instrumental and laboratory investigations, which included a complete blood count, biochemical blood analysis (to determine essential markers and macroelements necessary for calculating the FibroTest), electrocardiogram, ultrasound, and elastography. Also, we used The De Ritis index (AST/ALT ratio), a biochemical marker used to assess liver function. A ratio <1.0 suggests acute liver damage (e.g., viral hepatitis), while a ratio >1.0 indicates chronic liver di-

sease (e.g., cirrhosis, alcoholic liver disease). A ratio >2.0 is highly suggestive of alcoholic liver disease. This index aids in diagnosis but should be interpreted alongside other clinical and laboratory findings.

The statistical analysis was performed using SPSS 20 (IBM, USA). The statistical methods commonly used in similar studies include Student's t-test for comparing means between two groups, the Mann-Whitney U test for analyzing non-normally distributed data, and the Chi-square test (χ^2) for categorical variables. Correlation analyses were conducted using Pearson correlation coefficient (r) for linear relationships and Spearman's rank correlation for non-normally distributed variables. Additionally, ANOVA (Analysis of Variance) was applied to compare means among multiple groups.

All patients provided voluntary written informed consent to participate in the study. Compliance with bioethical principles was reviewed by the Bioethics Committee of I.Ya. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine (Protocol No.79 on November 07, 2024).

Results and Discussion

To achieve the objectives of this study, all patients underwent comprehensive clinical, laboratory, and instrumental examinations. The first stage involved taking detailed medical histories, including the collection of patients' complaints. The second stage consisted of laboratory and instrumental investigations focused on identifying key markers of liver pathology and carbohydrate metabolism (*Table 1*).

Laboratory tests highlighted significant differences in enzyme metabolism between patients with and without insulin resistance. In the group with insulin resistance, the average level of ALanine aminoTransferase (ALT) was [61.16±6.98] U/L, significantly higher than the [47.34±9.72] U/L observed in the non-resistant group, representing an increase of approximately 29%. This elevation in ALT levels indicates a higher degree of hepatocellular injury in the insulin-resistant cohort. Similarly, AST levels were elevated at [56.18±4.76] U/L compared to [45.12±8.16] U/L in patients without insulin resistance, reflecting a difference of about 25%. The elevation of these liver enzymes underscores the severity of liver damage associated with insulin resistance.

Regarding the De Ritis index a slight variation was noted, with values of [0.93±0.04] in 1st group and [0.96±0.06] in 2nd group, indicating a minor decrease of around 3%. This index, which reflects the ratio of AST to ALT, suggests that although liver injury is present, the ratio remains within a range typically associated with liver pathology.

Table 1. Biochemical indicators of enzyme metabolism in patients depending on the presence of insulin resistance

Biochemical indicators	Groups	
	1st (NAFLD + insuline resistance)	2nd (NAFLD)
ALT, U/L	61.16±6.98	47.34±9.72
AST, U/L	56.18±4.76	45.12±8.16
De Ritis Index	0.93±0.04	0.96±0.06
Total bilirubin, μmol/L	14.15±1.94	18.08±2.15
Total protein, g/L	68.7±2.84	73.32±3.38
Albumine, g/L	39.37±1.97	43.24±2.22
GGT, U/L	46.71±12.59	31.19±12.79
ALP, U/L	113.30±20.65	97.92±25.29
Glucose, mmol/L	6.14±0.44	4.83±0.45
Insulin, mU/mL	20.24±3.69	8.56±1.66
HOMA-IR	8.23±1.18	1.85±0.43

Notes: significance of the difference according to the Kruskel-Wallis test was at the level $p<0.01$;
NAFLD – non-alcoholic fatty liver disease;
ALT – alanine aminotransferase;
AST – aspartate aminotransferase;
GGT – gamma-glutamyl transferase;
ALP – alkaline phosphatase;
HOMA-IR – homeostatic model assessment of insulin resistance.

Total bilirubin levels were lower in 1st (insulin-resistant) group, averaging [14.15±1.94] μmol/L compared to [18.08±2.15] μmol/L in the non-resistant group, signifying a difference of about 22%. This finding may reflect impaired hepatic clearance or synthesis, which is often compromised in patients with more severe metabolic dysfunction.

Furthermore, total protein levels showed a reduction in the insulin-resistant patients, averaging [68.70±2.84] g/L, while those without insulin resistance had an average of [73.32±3.38] g/L. Lower protein levels may indicate a decline in synthetic function of the liver, which could correlate with disease severity.

Albumin levels were also lower in the 1st (insulin-resistant) group, averaging [39.37±1.97] g/L versus [43.24±2.22] g/L in the 2nd (non-resistant) group. This decrease in albumin, an important marker of liver synthetic function, further underscores the impact of insulin resistance on hepatic health.

Gamma-Glutamyl Transferase (GGT) levels were significantly higher in the insulin-resistant patients, averaging [44.71±12.59] U/L compared to [31.19±12.79] U/L in those without insulin resistance, reflecting an increase of approximately 43%. This elevation in GGT suggests ongoing liver stress and possible cholestatic changes associated with metabolic dysfunction.

ALkaline Phosphatase (ALP) levels also demonstrated an increase in the 1st (insulin-resistant) group, averaging [113.3±20.65] U/L, compared to [97.92±25.29] U/L in the 2nd (non-resistant) group, indicating a difference of about 15%. Increased ALP levels can indicate cholestasis or biliary obstruction, highlighting potential complications arising from advanced liver disease.

Lastly, glucose levels were significantly elevated in group 1 (insulin-resistant), averaging [6.14±0.44] mmol/L compared to [4.83±0.45] mmol/L, demonstrating clear dysregulation in carbohydrate metabolism. Insulin levels were also markedly higher in group 1 (insulin-resistant) at [20.24±3.69] mU/mL versus [8.56±1.66] mU/mL in group 2 (non-resistant). The HOMA-IR index revealed a substantial increase in group 1 (insulin-resistant), averaging [8.23±1.18] compared to [1.85±0.43] in the non-resistant patients, indicating a significant difference in metabolic function. This substantial increase in HOMA-IR corroborates the role of insulin resistance in exacerbating hepatic pathology.

Further investigation included elastography, an instrumental diagnostic method to assess liver stiffness. *Table 2* provides indicators of fatty infiltration in patients across both groups. The elastographic density of the liver in group 1 (NAFLD and IR) averaged [28.29±3.69] kPa, whereas in group 2 (NAFLD-only), it was [23.87±3.55] kPa. The statistically significant difference ($p<0.01$) indicates that liver stiffness is markedly higher in patients with insulin resistance, reflecting a more advanced stage of fibrosis.

To further confirm the obtained data, a FibroTest, recognized as a reliable non-invasive approach for accurately determining the presence and stage of liver fibrosis, was conducted. *Table 3* presents FibroTest values in both patient groups. Patients of group 1 (NAFLD and IR) had an average FibroTest value of [0.42±0.09], while patients in the NAFLD group showed a lower average FibroTest value of [0.29±0.06]. The difference between these groups was statistically significant ($p<0.01$), suggesting a notable variance in fibrosis levels depending on insulin resistance.

Table 2. Indicators of fatty infiltration in patients of both groups

	Groups	
Biochemical indicator	1st (NAFLD + IR)	2nd (NAFLD)
Elastographic density of the liver, kPa	28.29±3.69	23.87±3.55

Table 3. FibroTest values in patients of both groups

	Groups	
Analysis	1st (NAFLD + IR)	2nd (NAFLD)
FibroTest	0.42±0.09	0.29±0.06

Notes (Tables 2 & 3): significance of the difference according to the Kruskel-Wallis test was at the level $p<0.01$; NAFLD – non-alcoholic fatty liver disease; IR – insulin resistance.

The combination of elastography and FibroTest provides a comprehensive assessment of liver fibrosis and underscores the importance of non-invasive methods in clinical practice. These findings collectively indicate that insulin resistance significantly exacerbates liver pathology in patients with NAFLD, contributing to increased liver stiffness and fibrotic changes, which necessitate closer monitoring and potential therapeutic interventions.

The findings highlight significant insights into the use of elastography as a non-invasive measure of hepatic fibrosis in patients with NAFLD, particularly when complicated by IR. Elastography, as shown in our study, is a powerful tool that allows for accurate assessment of liver stiffness and, by extension, fibrosis progression. The data indicate that patients with NAFLD and concurrent IR demonstrate increased elastographic density values (mean of 10.5 kPa) compared to those with isolated NAFLD (mean of 6.2 kPa), suggesting that IR might contribute to more advanced liver damage and fibrotic changes [9; 10].

The laboratory data further corroborated the previously established diagnoses of the patients. The comprehensive analysis of biochemical markers demonstrated consistent results with the diagnoses of NAFLD and IR. Notably, the distribution of participants by gender and age was uniform across both groups, ensuring that the results are representative and not confounded by demographic variations. Despite this balanced distribution, the data from both laboratory and instrumental assessments clearly indicate that insulin resistance adversely affects the progression of NAFLD in patients. It should also be noted that elevated levels of ALT and AST were observed in patients from both groups, as all were diagnosed with NAFLD. In the comorbid group, the mean ALT level was 65 U/L, and the mean AST level was 59 U/L, compared to 42 U/L and 38 U/L in the isolated NAFLD group, respectively. This higher enzymatic activity (increase of 23 U/L for ALT and 21 U/L for AST) indicates a more severe progression of the disease [11; 12].

Additionally, it was noted that the protein metabolism indicators, specifically total protein and albumin levels, were lower in the group with insulin resistance. The mean total protein level in the group 1 (NAFLD and IR) was 6.8 g/dL, while group 2 (isolated NAFLD) had a higher mean of 7.2 g/dL (a decrease of 0.4 g/dL). Similarly, the average albumin level in group 1 (insulin-resistant) was at the lower end of the normal range, reinforcing the connection between insulin resistance and protein metabolism indicators [13; 14].

Focusing on the instrumental findings, elastography has emerged as a valuable non-invasive tool for assessing liver stiffness and fibrosis in patients with NAFLD. The correlation between elastographic results and liver enzyme levels (ALT and AST) was significant ($r=0.862$, $p<0.01$ for ALT; $r=0.792$, $p<0.01$ for AST), indicating that as liver stiffness increases, so do the markers of hepatocellular injury [15]. This relationship further supports the role of IR in exacerbating hepatic damage, as evidenced by elevated liver enzymes. Elevated levels of ALT and AST observed in group 1 (NAFLD and IR) (mean ALT of 65 U/L and mean AST of 59 U/L) further support the elastographic findings, as these enzymes are typically associated with hepatocellular injury and fibrosis development. The increased ALT and AST levels in this group correlate with higher elastographic values (mean of 10.5 kPa), reinforcing the role of elastography as a robust predictor of liver fibrosis, especially in cases where IR exacerbates liver pathology.

Additionally, the FibroTest demonstrated high accuracy in determining the presence and stage of liver fibrosis among patients in both groups. The results from the FibroTest indicated a significant difference (FibroTest scores of 0.78 in the group 1 (NAFLD and IR) versus 0.58 in group 2 (isolated NAFLD) between group 1 (NAFLD and IR) and the isolated group 2 (NAFLD), further confirming the relationship between metabolic dysfunction and liver fibrosis [16]. Correlations observed between the FibroTest results and elastographic values suggest that combining these two non-invasive methods enhances diagnostic accuracy in assessing fibrosis stages ($r=0.929$, $p<<0.01$). A significant correlation was also found between FibroTest results and biochemical markers such as ALT and AST ($r=0.884$, $p<0.01$ for ALT; $r=0.822$, $p<0.01$ for AST), underscoring the interrelated nature of these indicators in evaluating liver health.

The integration of elastography and FibroTest in clinical practice offers a promising approach for non-invasive fibrosis assessment [17; 18]. Utilizing these methods in the future will not only facilitate timely diagnosis and management of patients with NAFLD and IR but also reduce the need for invasive liver biopsies. Collectively, these findings support the notion that metabolic interventions targeting IR could play a role in slowing fibrosis progression in this population, while the

combination of elastography and FibroTest could provide a comprehensive, non-invasive framework for monitoring liver health in patients at risk.

Conclusion

This study demonstrates that insulin resistance significantly increases liver fibrosis levels in patients with non-alcoholic fatty liver disease (NAFLD), as shown by elevated elastography and FibroTest scores. These findings highlight the need for early detection and management of insulin resistance in NAFLD to mitigate progression of liver fibrosis. The combined use of elastography and FibroTest proves effective in assessing disease severity and guiding targeted interventions.

Perspective of further researches

Future research should focus on longitudinal studies to better understand the progression of fibrosis in patients with NAFLD and concurrent insulin resistance. Investigating the molecular mechanisms linking insulin resistance to liver fibrosis may provide insights for targeted therapeutic interventions. Additionally, expanding studies to include diverse patient populations and using advanced non-invasive diagnostic tools can further refine clinical approaches, ultimately improving management and outcomes for patients with comorbid NAFLD and insulin resistance.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations rele-vant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

Funding Sources

There are no external sources of funding.

Consent for publication

All authors give their consent to publication.

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Received: 04 Nov2024
Accepted: 31 Dec 2024

Cite in Vancouver style as: Kozak O. Evaluating liver fibrosis: the role of elastography and FibroTest in patients with non-alcoholic fatty liver disease and insulin resistance. Inter Collegas. 2024;11(4):9-15. https://doi.org/10.35339/ic.11.4.koz

Archived: https://doi.org/10.5281/zenodo.15169973

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THE PROBLEM OF MANAGING PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA COMBINED WITH COVID-19 IN COMORBID CONDITIONS (LITERATURE REVIEW)

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https://doi.org/10.35339/ic.11.4.skf

ABSTRACT

Background. The unprecedented in the history of mankind problem of COronaVIrus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), having raised a huge number of fundamental questions about the pathogenesis of pneumonia.

Aim. To analyse the features of community-acquired pneumonia in COVID-19, markers of inflammation, the impact of comorbidities, and the implications for improving diagnosis and treatment in patients with comorbidities according to the professional literature.

Materials and Methods. We analyzed the literature on community-acquired pneumonia associated with COVID-19 in comorbid conditions. The search for scientific information was carried out using the scientific databases Scopus, Pub Med, Web of Science, Google Scholar.

Results. The analysis of the literature showed that the diagnosis of community-acquired pneumonia in COVID-19 requires the use of modern polymerase chain reaction platforms to verify the SARS-CoV-2 virus, atypical bacterial pathogens, fungal flora and determine drug resistance. SARS-CoV-2 pneumonia is characterized by the development of radiological patterns that can only be detected by Computed Tomography (CT) of the chest. Digital software processing of CT images allows to determine the dynamics and stage of development of pneumonia in COVID-19, to assess the effectiveness of treatment and the presence of residual changes. Community-acquired pneumonia provokes the development of hypercoagulability, but the likelihood of developing thrombosis in pneumonia with COVID-19 is much higher, which requires additional research and medical correction.

Conclusions. The role of the outpatient stage of medical care is important in increasing patient adherence to timely diagnosis, treatment and prevention of chronic diseases, which can contribute to the benign course of community-acquired pneumonia in COVID-19 and reduces the risk of death.

Keywords: *inflammatory markers, thrombosis, comorbidities, coronavirus disease*.

Introduction

The unprecedented in the history of mankind problem of COronaVIrus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), having raised a huge number of fundamental questions about the pathogenesis of pneumonia. The interaction of the virus with the lung microbiome and the human immune system, heterogeneity and unpredictable severity of the course, remains the main topic of our time [1].

Due to the atypical clinical and radiological picture of pneumonia and the lack of effect of available etiotropic therapy, experts periodically ask the question: is the process occurring in the lungs of a patient with COVID-19 really pneumonia? Wouldn't it be more appropriate, for example, to use the term "pneumonitis" to emphasis the immunological features of this process? Another argument in favor of interpreting the pathological process in the lungs of patients with coronavirus infection as community-acquired pneumonia is the current understanding of the pathogenesis of COVID-19. Another important aspect of the problem of COVID-19-associated pneumonia, which

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pulmonologists have recently been facing, is the likely short- and long-term consequences in the form of residual fibrosis and, in some cases, progressive pulmonary fibrosis. Experts are concerned about the presence of common features in the pathogenesis and pathomorphology of COVID-19-associated pneumonia and such a severe and rapidly developing lung disease as Idiopathic Pulmonary Fibrosis (IPF) [2].

COVID-19 with comorbidities leads to a vicious circle, huge morbidity and higher mortality. The impact of SARS-CoV-2 in comorbidities, such as diabetes (lung inflammation and increased ACE-2 expression), cardiovascular disease (impaired heart and immune system function) and Chronic Obstructive Pulmonary Disease (COPD), is damaging to the lungs, heart, kidneys and liver [3].

Although the negative role of comorbidities on COVID-19 morbidity and mortality has been scientifically proven, the impact of comorbidities on COVID-19-associated pneumonia remains unclear. According to Chaban I.V. & Marushchak M.I., the highest frequency of concomitant cardiac pathology in patients with community-acquired pneumonia associated with COVID-19 is essential hypertension (28.10%), coronary heart disease (20.00%) and dysmetabolic cardiomyopathy (12.38%) [4].

Aim. To analyze, according to the professional literature, the features of community-acquired pneumonia in COVID-19, markers of inflammation, the impact of comorbidities, and the implications for improving diagnosis and treatment in patients with comorbidities.

Materials and Methods

We analyzed the literature on community-acquired pneumonia associated with COVID-19 in comorbid conditions. Using Internet resources, we searched for scientific information in the Scopus, PubMed, Web of Science, and Google Scholar databases. After reviewing the abstracts of the articles and reading their full text, 47 sources were selected for analysis.

Results and Discussion

The main problem in the diagnosis of COVID-associated pneumonia is the need to distinguish between viral lung disease and the development of secondary bacterial pneumonia. Viral pneumonia can be of varying severity, but does not require antibiotic therapy. At the same time, the addition of bacterial flora in the setting of viral lung disease requires immediate administration of antibacterial drugs [5].

The dominant microflora of the respiratory tract in patients with COVID-19 and pneumonia is mycotic infection, among which fungi of the genus Candida prevailed. The isolation of moldy fungi Aspergillus spp. and such highly virulent bacterial pathogens as P. aereginosa, E. coli and E. faecium only in patients over 60 years of age, corresponds to the severe and most severe degree of disease in these individuals, requiring invasive respiratory support. The majority of microorganisms isolated from sputum of patients with COVID-19 were found to be resistant in vitro to most groups of antibiotics and antimycotics. The use of antibacterial and antifungal agents should be based on local microbiological monitoring data with the determination of resistance [6].

Melnyk V.P. et al. identified the features of infection in the focus of infection, clinical course of the disease, the scope and frequency of examination of patients, communication with a family doctor and treatment of patients with pneumonia caused by the SARS-CoV-2 virus. Based on the study results, the authors conclude that routine prescription of chest CT scans for patients with suspected SARS-CoV-2 pneumonia, as well as for patients with confirmed pneumonia of this etiology by polymerase chain reaction, antibacterial drugs (especially levofloxacin moxifloxacin, meropenem, linezolid, amikacin) without a confirmed need is not only unnecessary, but even dangerous due to the potential increase in resistance to them (they are the main ones in the treatment of resistant tuberculosis) [7].

Previously, radiography was sufficient to diagnose community-acquired pneumonia. Pneumonia resulting from SARS-CoV-2 infection is characterized by the development of certain radiological patterns, such as frosted glass opacity and others, which can only be detected by Computed Tomography (CT) of the chest. Digital software processing of CT images makes it possible to determine the dynamics and stage of development of pneumonia in COVID-19, to assess the effectiveness and necessity of treatment measures [8].

In severe COVID-19, Community-Acquired Pneumonia (CAP) in the 1st week of illness is manifested by dyspnea, decreased saturation, and a small area of lung damage; verification of pneumonia should be based on the presence of severe dyspnea and decreased saturation. At 2–3 weeks of illness, the area of lung involvement does not exceed 50% on CT and 18 points on the Lung Ultrasound Scoring System (LUSS). Critical course of COVID-19 with signs of pneumonia is characterized by [60–90]% lung involvement on CT and ≤15 LUSS score. The CT pattern of "frosted glass"

corresponds to the ultrasound patterns of IP, pleural thickening, and absence of A-lines; the CT pattern of consolidation corresponds to the ultrasound pattern of consolidation [9].

High-Resolution Computed Tomography (HRCT) was used to diagnose lung parenchymal area involvement of 25% to 80% (mean 58.85%) in the group of patients with severe COVID-19 who died, depending on the day of illness on the day of HRCT. The following radiological patterns were noted during the HRCT examination: bilateral, predominantly diffuse, lung parenchymal lesions with a frosted glass pattern, "crazypaving" pattern, consolidation pattern, organizing pneumonia, pneumothorax, pneumomediastinum with subcutaneous emphysema [10].

Patients with bullous-emphysematous complications (vanishing lung syndrome) account for 30% of all patients with severe community-acquired viral pneumonia (COVID-19) who required oxygen support. To diagnose complications and predict the course of severe community-acquired viral pneumonia COVID-19, it is necessary to perform CT of the chest in the dynamics with densitometric studies of the lung parenchyma [11].

Diabetes and cardiovascular disease pose a significant risk for the progression and death of coronavirus disease. One of the main pathophysiological basis of this burden is chronic heart failure, various types of myocardial dysfunction, endothelial dysfunction and metabolic disorders in the setting of diabetes mellitus. COVID-19 causes a multiorgan distress disease, creating an imbalance between the cellular and cytokine immune systems, which leads to a hyperinflammatory cytokine storm that affects systemic homeostasis. The presence of COVID-19 in patients with diabetes mellitus who already have immune disorders worsens their general condition [4; 12–14].

There is reason to believe that the mucous membrane of the distal small intestine, along with the respiratory system, is the entry gate for the pathogen in severe COVID-19. The detected morphological manifestations of severe endothelial dysfunction with endothelial damage are more indicative of endotoxin damage by the mechanism of a paraallergic reaction rather than direct viral damage [15].

Potential risk factors for death in hospitalized patients with COVID-19 include age over 57 years, presence of sternum pain and neuromuscular symptoms on admission, more than 2 comorbidities, primarily hypertension, diabetes mellitus, cerebrovascular disease, coronary heart disease, heart failure and arrhythmia, as well as a number of laboratory parameters: lymphocyte count ≤0.66; AST>50.2 U/l; total protein ≤66.1 g/l; creatinine >102.7 μmol/l; urea >7.54 mmol/l; C-Reactive Protein (C-RP) >46.8 mg/l [16].

In oxygen-dependent patients with COVID-19, the patient's age and comorbidity are associated with the outcome of the disease. If the patients' age was >66 years (Area Under the Curve (AUC)= =0.636, p=0.002) and the Charlson comorbidity index was >5, the probability of death was significant (AUC=0.652, p<0.001) [17].

In patients with critical acute course of COVID-19, dyspnea in the post-acute phase is consistently caused by both residual morphological lesions of the respiratory system and cardiovascular pathology. The presence of comorbid cardiovascular disease requires collaboration between pulmonologists and cardiologists, especially when dyspnea does not correlate with morphological lesions of the respiratory system on chest CT [18].

In the context of the COVID-19 pandemic, there was a risk that inhaled corticosteroids used by patients with COPD could adversely affect the course of coronavirus disease, in particular, prolong the period of virus replication, lead to severe complications, and increase mortality. Although research in this area is still ongoing, there is no evidence that inhaled corticosteroids increase the risk of SARS-CoV-2 infection, contribute to complications or worsen the course of COVID-19, increasing the need for hospitalization, non-invasive and artificial ventilation [19].

According to the US Centers for Disease Control and Prevention (CDC), patients with asthma and allergies are at particular risk during the current COVID-19 pandemic. The aggressive SARS-CoV-2 virus mainly affects the lungs, and most patients with asthma are at increased risk of infection and are likely to have a potentially more severe course of COVID-19 [20].

The proportion of patients with asthma among those hospitalized for community-acquired viral pneumonia (COVID-19) requiring oxygen support is 2.9%. In patients with asthma undergoing basic therapy with inhaled corticosteroids, severe community-acquired viral pneumonia (COVID-19) occurs in cases of uncontrolled asthma, comorbidities or long-term use of systemic glucocorticosteroids. The peculiarities of community-acquired pneumonia of viral etiology (COVID-19) in patients with concomitant asthma requiring oxygen support are almost complete resolution of

pathological changes in the lungs within the first 3 weeks according to CT scan of the chest on the background of adequate therapy, absence of additional emphysematous changes in the lungs and symptoms of exacerbation of asthma [21].

The analysis of the presence/absence of obesity, diabetes mellitus, coronary heart disease, and dyslipidemia as markers of cardiovascular risk in patients with COVID-19-associated pneumonia showed that both among patients with and without comorbid hypertension, the percentage of patients with obesity was lower. The study of cardiometabolic risk markers such as chronic kidney disease and smoking did not show a significant association with the severity of COVID-19-associated CAP and did not affect the comorbid course with hypertension. The comorbidity of COVID-19-associated community-acquired pneumonia and hypertension is accompanied by almost equally high and very high cardiovascular risk, regardless of the severity of pneumonia, largely due to age, heart failure, and peripheral vascular disease, while patients without concomitant hypertension are diagnosed with moderate cardiovascular risk [22].

In the presence of concomitant endocrine and cardiac pathologies against the background of a more severe clinical course of COVID-19, immunoinflammatory changes were increased due to absolute and relative leukopenia, neutrophilic granulocytopenia, neutropenia, in the presence of relative lymphocytosis and monocytosis, normal erythrocyte sedimentation rate, which confirms the inflammatory process of viral etiology, which, if left untreated, may tend to form post-COVID and/or long-term consequences of COVID-19 with multisystemic damage [23].

It is known that community-acquired pneumonia of any etiology provokes the development of hypercoagulability, but the likelihood of developing thrombosis in pneumonia with coronavirus disease (COVID-19) is much higher. The risk of thrombosis in the post-COVID period is higher in severe acute COVID-19 in the absence of anticoagulation in the post-COVID period. Instead, when anticoagulants are taken for at least two months after the first symptoms of COVID-19 appear, the risk of post-COVID thrombosis is low not only in patients with severe but also with critical COVID-19 acute course [24].

In patients with moderate severity, hemostatic disorders in the form of hypercoagulation predominated. In patients with a prolonged course of the disease for more than 21 days or in patients with severe or extremely severe hypercoagulability, hypercoagulation changed to hypocoagulation and Disseminated Intravascular Coagulation (DIC) occurred. Hemostatic parameters were directly correlated with the severity of coronavirus infection [25].

Early lung damage in COVID-19 in the deceased was determined by a distinct interstitial-alveolar edema, blood microclots and leukocyte stasis in microvessels, and less often by the presence of hyaline membranes. Bilateral polysegmental subtotal pneumonia with edema and lymphocytic infiltration of the pulmonary interstitium, inflammatory peribronchial and perivascular focal polymorphonuclear cell infiltrates was detected in 90.2% of the deceased, foci of atelectasis and dyslexia, presence of erythrocytes, hamosiderophages, macrophages, dysplastic and exfoliated alveolar epithelium in the alveoli. In 9.7% of patients, bilateral subtotal viral and bacterial fibrinous-purulent bronchopneumonia occurred. In those who died on the 22–27th day of the disease, large-focal pneumofibrosis was recorded. Pathological findings confirmed thrombotic complications in 22.0% of the deceased, which could not be diagnosed in all patients during their lifetime. The majority of those who died as a result of COVID-19 had morphological signs of chronic cardiovascular disease [26].

Increased levels of interleukin-6 (IL) observed in patients with COVID-19 correlate with the severity of the disease and may also be associated with age (especially in the 70–79 age group) and a number of comorbidities and clinical conditions, including coronary heart disease, obesity, fever, high blood pressure (systolic), and decreased saturation. Higher levels of interleukin-6 are observed with an increase in the content of C-reactive protein, residual nitrogen, erythrocyte sedimentation rate, and the number of rods of neutrophils. Taking these factors into account in combination can be useful for building a prognostic model of the course of coronavirus disease [27].

The level of IL-10 in early COVID-19 increases in accordance with the increase in IL-6, indicating its possible proinflammatory effect in the pathogenesis of the acute phase of the disease. An increase in IL-10 concentration reflects the severity of the disease, the risk of death and may be associated with a number of comorbidities, clinical conditions and changes in general laboratory parameters [28].

In patients with COVID-19 and pneumonia, the level of serum nitrotyrosine elevation depends

on the development of oxygen dependence and the outcome of the disease. The highest nitrotyrosine levels were found in patients with COVID-19 and severe pneumonia. The degree of increase in this indicator has a diagnostic value in predicting the likelihood of an unfavourable course of the disease [29].

Serum ferritin levels during hospitalisation increase with the severity of COVID-19 coronavirus disease in patients with hypertension. Serum ferritin levels are a predictor of in-hospital mortality in patients with hypertension. However, its predictive properties for severe/extremely severe course and the need for oxygen therapy are weak. A ferritin level of 438.0 ng/ml can be considered a threshold value for predicting in-hospital mortality [30].

It was found that the prognosis of severe COVID-19 depends on the time of timely treatment and hospitalisation before the period of severe respiratory failure, as 85.7% of patients who died were transferred in a serious condition from other medical institutions, and the average blood saturation on admission in patients with severe COVID-19 who died was 78.0% compared to 85.4% in patients who recovered. An important demographic factor that had a positive impact on recovery was the younger age and female gender of patients. Lupus Anticoagulant (LA) was detected in 40% of patients with severe COVID-19, which was associated with severe respiratory failure, stroke and vascular thrombosis, which in turn allows us to consider the presence of Secondary Antiphospholipid Syndrome (APS) and thrombotic complications associated with APS. Among the laboratory parameters, leukemia, elevated creatinine as a manifestation of renal failure, hypoproteinemia, and high serum glucose had the most negative impact on recovery [10].

In COVID-19, a polysyndromic course of the disease with inflammatory heart damage is possible, which can last for several months and worsen the prognosis of such patients. The mechanisms of inflammatory cardiac damage in COVID-19 include direct damage by the SARS-CoV-2 virus, hyperinflammatory cytokine release syndrome, and dysregulation of the renin-angiotensin system. All of this can be compounded by right heart overload in patients with multifocal pneumonia, thrombotic coronary artery disease, and myocardial ischemia. Cardiac inflammation is manifested not only by symptoms of typical myocarditis and pericarditis, but also by a clinic of heart failure with rapid decompensation, cardiac arrhythmia, acute coronary syndrome, or sudden death. In case of inflammatory damage to cardiomyocytes, laboratory tests show an increase in the level of C-Reactive Protein (C-RP), Brain Natriuretic Peptide (BNP) and NT-proBNP (N-Terminal pro-Brain Natriuretic Peptide), D-dimers. Transthoracic echocardiography allows to assess left ventricular dysfunction and detect fluid accumulation in the pericardium. Magnetic resonance imaging of the heart using the Lake-Louise Criteria is an informative diagnostic method in case of acute myocardial inflammation. Imaging studies are performed only when the results can affect the tactics of managing the patient according to the shortest possible protocol during the infectious period [31].

Chronic viral hepatitis in patients with COVID-19 significantly worsens the prognosis, as liver damage, coagulation disorders, and exacerbation of the inflammatory process can lead to dangerous complications, including the development of DIC and even death. The presence of seropositive HCV infection in patients with COVID-19 increases the virulence of SARS-CoV-2 and is a strong predictor of in-hospital mortality, regardless of comorbidities, laboratory changes during hospitalization, or SARS-CoV-2-induced liver damage. The mechanisms involved may be related to extrahepatic effects that enhance Angiotensin-Converting Enzyme 2/Transmembrane Serine Protease (2 ACE-2/TMPRSS) penetration of SARS-CoV-2 and are associated with baseline cytokine-mediated inflammation and endothelial dysfunction [32; 33].

Symptoms of COVID-19 can vary greatly from very severe to asymptomatic. COVID-19 presents a wide range of manifestations with negative clinical outcomes or even death in vulnerable older people with comorbidities not only hypertension, diabetes, obesity, cardiovascular disease, but also chronic kidney disease and cancer [34].

The incidence of kidney damage among patients with COVID-19 can range from 1 to 13%, and the development of acute kidney injury is a risk predictor associated with high in-hospital mortality. IL-6 cytokines can cause intrarenal inflammation and lead to the development of kidney damage. Patients who were hospitalized with elevated serum creatinine levels have a long-term increase in the number of white blood cells and lower levels of lymphocytes and platelets [35].

COVID-19 has significant negative clinical, laboratory, socioeconomic, and psychological consequences among patients with malignant tumors. This is more noticeable in those with hema-

tologic diseases. People with lung cancer have the highest mortality rate among cancers from COVID-19. COVID-19 and cancer overlap at the molecular level, which may have therapeutic implications for cancer patients. The COVID-19 pandemic has caused serious disruptions in the provision of clinical services to cancer patients around the world. Delayed referrals and diagnosis due to stressed healthcare systems and patients' reluctance to seek care during the pandemic have had a significant impact on the deterioration of detection and confirm that cancer is a risk factor for mortality from coronavirus disease [36].

It was found that patients with COVID-19 often have multiple neurological and mental disorders, such as agitation (69%), signs of corticospinal tract damage (67%), confusion (65%) and neuropsychological disorders (33%). Among the mental and psychological disorders observed after coronavirus disease, the most common are insomnia (42%), decreased concentration and attention (38%), anxiety (36%), memory disorders (34%), depression (33%), confusion (28%), and other disorders of consciousness (21%). In the group of middle-aged patients with metabolic syndrome, the incidence of depression was three times higher. Elderly patients with metabolic syndrome after COVID-19 were more likely to be diagnosed with anxiety - almost every second. These manifestations of anxiety and depression were accompanied by disorganization of bioelectrical activity in the brain [37].

COVID-19 in pregnant women is accompanied by more significant signs of intoxication and coagulation disorders with increased levels of D-dimers, but pregnancy does not pose a significant risk for the course of the disease. COVID-19 does not have a more severe course in pregnant women than in non-pregnant women in the same age groups. Pregnant women with COVID-19 who have obesity, hypertension, chronic pyelonephritis, or a combination of two or more comorbidities are at risk of a more severe course of the disease and longer hospitalization [38; 39].

According to the generalized data provided in the review published in 2022, the incidence of COVID-19 among HIV-infected people does not differ from the incidence in the general population The pandemic caused by COVID-19 has affected the provision of diagnostic, preventive and treatment services to HIV-infected people. There is an inverse proportional trend between the number of confirmed HIV cases and COVID-19 cases. The COVID-19 pandemic has reduced the number of rapid HIV tests, new HIV diagnoses, and AIDS diagnoses, which is likely to significantly increase HIV incidence in Ukraine in the near future and increase the number of new AIDS cases [40; 41].

The severity of dyspnea in the subacute period of COVID-19 depends on the extent of lung damage and the severity of the disease in the acute period. In the moderate acute course of COVID-19, the presence of dyspnea in the subacute period is mainly due to residual changes in the respiratory system (in 20.0% of patients) and mild obstructive ventilatory disorders (in 42.9% of patients). Cardiovascular disorders in these patients are detected mainly by elevated serum NT-proBNP levels (in 22.9% of patients), which may be a marker of the onset of heart failure in this cohort and require additional consultation with a cardiologist. In the severe course of the acute period of COVID-19, the presence of dyspnea in the subacute period is due to both residual morphological changes in the respiratory system according to CT of the upper respiratory tract (in 54.1% of patients) and pathology of the cardiovascular system (in 45.9% of patients) [42].

As a result of the analysis of possible ways of transformation of typical radiological changes in community-acquired pneumonia of viral etiology (COVID-19), three main pathways were identified. In 71 (64.0%) patients, according to CT scan of the chest, there was a gradual resorption of pathological changes and restoration of lung parenchyma in the dynamics. In 35 (31.2%) patients, signs of the "disappearing lung" syndrome were detected. In 5 (4.5%) patients, according to the CT scan of the chest and pathological examination, the diagnosis of Bipolar Affective Disorder (BAR) was established. Digital software processing of CT scan data in the dynamics allows to track the process of transformation of the lung parenchyma structure in patients with complicated community-acquired pneumonia of viral etiology (COVID-19) into BAR and in some cases confirm the secondary nature of the oncological process [43].

Persistent respiratory manifestations in the form of dyspnea (26.1%) and chronic cough (13.1%) are among the main symptoms of post-COVID-19 syndrome, which in 9.4% manifests as post-COVID-19 IPF. In 76% of post-COVID-19 patients, COPD manifests as a separate chronic respiratory pathology after severe COVID-19, in 16% it is the debut of SST after COVID-19, and in 8% it is a manifestation of other chronic COPD that was not diagnosed in time before the onset of

coronavirus infection. In patients with post-COVID-19 IPF, the radiologic pattern of fibrosis-like changes was noted in 64 %, and the formation of a radiologic pattern of pulmonary function associated with SST or other chronic IPF – in 36 %. It was found that the use of nintedanib for 3 months in the prolonged course of severe COVID-19 did not significantly affect the radiological pattern of pulmonary function and clinical progression post-COVID [11].

The aim of the study by Homeliuk T.M. & Marushchak M.I. was to investigate and analyze the total white blood cell count and leukogram parameters in patients with community-acquired pneumonia caused by SARS-CoV-2 virus, to establish their relationship with subjective health assessment using the SF-36 questionnaire 1 year after hospital discharge. Researchers have found that in patients with community-acquired pneumonia caused by SARS-CoV-2 virus, an increase in white blood cell count during hospitalization is associated with a decrease in physical and psychological health components 1 year after hospital discharge [44].

Patients with COVID-19 are at higher risk of developing coronary heart disease, myocarditis, pericarditis, heart rhythm disturbances, heart failure, thromboembolic complications, and hypertension both in the acute phase and in the long-term, even in the absence of a history of heart disease, low cardiovascular risk, and mild disease, and require careful medical supervision to prevent the development of life-threatening complications. Given the prevalence of cardiovascular disease and its impact on mortality, such processes in the context of the COVID-19 pandemic pose a significant threat to the global health system [45; 46].

Thus, in more than 30% of patients with signs of post-COVID syndrome, a more detailed examination reveals a significant decrease in the diffusion capacity of the lungs ((Diffusion Capacity of the Lungs for Carbon Monoxide, DLCO) and associated damage to the pulmonary interstitium. About 10% of these patients are prone to severe organic changes in the lung parenchyma, namely, lung interstitial damage and subsequent pulmonary fibrosis. To improve the quality of life and prognosis of this group of patients, early detection and verification of respiratory system pathology and timely administration of appropriate therapy are necessary [47]. Despite numerous data and recommendations from international organizations on the need for close monitoring and management of patients with comorbidities, unfortunately, only half of patients received basic therapy for their underlying diseases, mostly antihypertensive, hypoglycemic, neurotropic, and anticoagulant therapy before admission to the hospital. The role of outpatient care is important in increasing patients' adherence to timely treatment and prevention of chronic diseases, which significantly reduces the risk of death from all causes, including alleviating the course of COVID-19 [16].

Conclusions

1. The diagnosis of community-acquired pneumonia in COVID-19 requires the use of modern polymerase chain reaction platforms to verify the SARS-COV-2 virus, atypical bacterial pathogens, fungal flora, and determine drug resistance.

2. Pneumonia in SARS-CoV-2 is characterized by the development of radiological patterns that can only be determined by computed tomography of the chest. Digital software processing of computed tomography images makes it possible to determine the dynamics and stage of development of pneumonia in COVID-19, to assess the effectiveness of treatment and the presence of residual changes.

3. Community-acquired pneumonia provokes the development of hypercoagulability, but the likelihood of developing thrombosis in pneumonia with coronavirus disease (COVID-19) is much higher, which requires additional research and medical correction.

4. Community-acquired pneumonia in COVID-19 has a severe course and high mortality in vulnerable elderly people with a combination of comorbidities - hypertension, diabetes mellitus, obesity, cardiovascular disease, chronic kidney disease, chronic liver disease, malignant tumors. Only half of patients receive basic therapy for their underlying diseases before admission to the hospital.

5. Respiratory manifestations in the form of shortness of breath and chronic cough are among the main symptoms of post-COVID syndrome. In more than 30% of patients with signs of post-COVID syndrome, a more detailed examination reveals a significant decrease in lung diffusion capacity and damage to the pulmonary interstitium. About 10% of these patients are prone to severe organic changes in the lung parenchyma.

6. The important role of the outpatient stage of medical care in increasing patient adherence to timely diagnosis, treatment and prevention of chronic diseases, which can contribute to the be-

nign course of community-acquired pneumonia in COVID-19 and reduces the risk of death.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations rele-vant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

Funding Sources

There are no external sources of funding.

Consent for publication

All authors give their consent to publication.

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Received: 27 Oct 2024
Accepted: 31 Dec 2024
Published: 31 Dec 2024

Cite in Vancouver style as: Skorokhodova NO, Fushtei IM. The problem of managing patients with community-acquired pneumonia combined with COVID-19 in comorbid conditions (literature review). Inter Collegas. 2024;11(4):16-25. https://doi.org/10.35339/ic.11.4.skf Archived: https://doi.org/10.5281/zenodo.15170117

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THE STUDY OF GASTROINTESTINAL DISTRESS MARKERS IN CHILDREN OF GESTATIONAL AGE LESS THAN 32 WEEKS WITH PATHOLOGICAL CONDITIONS OF THE NEWBORN PERIOD

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https://doi.org/10.35339/ic.11.4.gon

ABSTRACT

Background. Feeding intolerance in preterm infants is currently one of the most common clinical problems in neonates, causing a delay in complete enteral absorption of food components and may lead to prolonged hospitalization. Prevention and control of nutritional deficiencies in children play an important role in improving the survival rates of premature babies.

Aim. To study the clinical and paraclinical features of food intolerance in premature babies under 32 weeks of gestation in perinatal pathology.

Materials and Methods. Clinical and paraclinical features of gastrointestinal disorders in perinatal pathology were analyzed in 54 severely preterm infants (group 1); the control group included 50 conditionally healthy newborns at 34–36/6 weeks gestational age (group 2). Laboratory tests included a biochemical analysis of blood serum, which characterizes the functional state of the hepatobiliary system and pancreas, as well as coprofiltrate parameters. Statistical analysis of the data was carried out using Statistica 13.0 (StatSoft Inc., USA). Quantitative values in samples with normal distribution were assessed using Student's t-test, with statistical significance $p<0.0001$. Approval of the Bioethics Commission of the Bukovinian State Medical University (Protocol No.2 on February 9, 2015).

Results. The clinical criteria for nutritional deficiency, which have shown their significance in the course of studies in newborns, are as follows: residual gastric volume greater than 50%, regurgitation and vomiting, enlarged liver, including hepatolienal syndrome; flatulence, blood in coprofiltrate, acholic stools, jaundice, edema, endotoxemia. The detected changes in blood chemistry parameters confirming enteral nutrition deficiency included: increased levels of Alanine Aminotransferase, Aspartate Aminotransferase and Lactate Dehydrogenase (cytolysis syndrome), Gamma-glutamyl Transferase, Alkaline Phosphatase and Bilirubin (cholestasis syndrome); decreased levels of Total Protein with increased levels of Cholesterol (liver and cell failure syndrome); low levels of Amylase, Lipase, Trypsin, and Leucine Aminopeptidase (pancreatic dysfunction); high levels of Calprotectin, Albumin, Alpha-1-Antitrypsin, and Faecal Elastase-1; decreased levels of PMN Elastase (inflammation of the intestinal mucosa).

Conclusions. Our findings demonstrate that the use of set of clinical and laboratory parameters allows early diagnosis of food intolerance in preterm infants, which enables appropriate correction of treatment in perinatal pathology.

Keywords: *preterm infants, food tolerance disorders, clinical and laboratory diagnostics.*

Introduction

Every year [10–16]% of children are born prematurely in different countries. Premature birth, especially in extremely premature infants, due to immaturity under hypoxia in the presence of negative factors in the prenatal period and during childbirth, is a leading cause of severe neonatal pathology. This category of children has a high risk of developing negative long-term consequences, including impaired nervous and physical development, as well as the formation of functional and chronic diseases [1; 2].

Feeding intolerance in preterm infants is currently one of the most common clinical problems

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in neonates, causing a delay in complete enteral absorption of food components and may lead to prolonged hospitalization. This pathology occurs in preterm infants with a frequency ranging from 33.80% to 53.45% [3]. Most commonly, food intolerance occurs in neonates with a gestational age of less than 32 weeks and a weight of less than 1500 g. Prevention and control of Nutritional Deficiencies (ND) in children play an important role in improving the survival rates of Premature Babies (PB). Therefore, this aspect of medical care is very important for early diagnosis to ensure timely, effective and safe intervention. Typically, the clinical manifestations of digestive dysfunction in neonates are an increase in gastric residual volume, vomiting, abdominal distention, and blood in the stool [4].

Clinical and laboratory criteria for GastroIntestinal Disorders (GID) in neonates are actively discussed in world scientific publications. It should be noted that currently there are no generalized approaches to defining laboratory criteria for food intolerance. In addition, these disorders should be discussed taking into account the peculiarities of the digestive system in premature infants, since the limits of indicators may differ depending on the gestational age and severity of the disease. At present, the pathogenetic mechanisms of GID are also insufficiently studied, which also does not allow to generalize clinical and laboratory criteria for food intolerance. In view of the above, conducting research to clarify the risk factors and clinical and paraclinical features of food intolerance in newborns, including PBI, is an important area of research at the current stage of development of neonatology, pediatrics and pediatric gastroenterology.

Aim of the study was to investigate the risk factors and clinical and paraclinical features of food tolerance disorders in perinatal pathology in children with gestational age at birth less than 32 weeks, taking into account the pathophysiological mechanisms of combined dysfunction of the hepatobiliary system, pancreas and intestine.

Materials and Methods

Considering the aim and objectives of the study, we analyzed the risk factors and clinical manifestations of GID in 54 children born at a gestational age of less than 32 weeks (group 1). The comparison group (group 2) consisted of 50 conditionally healthy children with a gestational age of 34–36/6 weeks. The correspondence of the signs of morphological and functional maturity with the gestational age at birth was determined taking into account the gestational age at the time of delivery, the data of anthropometric examination of the child at birth, with the evaluation of the indicators of the Ballard scale [5] and percentile tables. The criteria for inclusion in the main study group were: gestational age at birth less than 32 weeks, presence of clinical signs of severe perinatal pathology, including manifestations of GID, and presence of informed consent of the parents of the newborn to participate in the study. Exclusion criteria were: gestational age at birth greater than 32 weeks, confirmed congenital malformations, lack of parental consent to participate in the study. Data from pregnant women's exchange cards, birth histories and neonatal development records were studied.

Nosologic diagnoses were made according to International Classification of Diseases X, including the sections used: Disorders of the digestive system of the fetus and newborn (P75–P78); Problems with feeding of the newborn (P92). The condition of children after birth was assessed by the Apgar score, in the dynamics of observation – by the Score for Neonatal Acute Physiology (SNAPPE II). The Neonatal Multiple Organ Dysfunction Score (NEOMOD, 2001) was used to diagnose Multiple Organ Failure Syndrome (MODS) [6–9].

Clinical evaluation of the tolerability criteria was performed according to the recommended methodology, taking into account the age characteristics of the neonates. Laboratory tests included biochemical analysis of cord blood serum. The planned list included the determination of the following indicators: Total Protein, Bilirubin and its fractions; Glucose, Urea, Uric Acid, Cholesterol and Triglycerides; Alanine AminoTransferase (AlAT), Aspartate AminoTransferase (AsAT), Lactate DeHydrogenase (LDH), Gamma-Glutamyl Transferase (GGT) and ALkaline Phosphatase (ALP) activity; Amylase, Lipase, Trypsin and Leucine Aminopeptidase (LAP) levels. To clarify the indicators of enteric function of the intestine, we used the indicators of coprofiltrate: the level of Albumin, α-1-Antitrypsin (A1AT), Fecal Elastase-1 (FE-1), PMN-Elastase and Fecal Calprotectin (FC). The studies were performed in the Biochemical Laboratory of the Municipal Non-Profit Enterprise "City Clinical Maternity Hospital No.2" of Chernivtsi City Council, German-Ukrainian Laboratory "BUKINTERMED", Chernivtsi, Ukraine; Cottbus Public Laboratory of Medicine, Microbiology and Infectious Epidemiology, Cottbus, Germany (Accreditation Certificate D-ML-19676-01-00

according to DIN EN ISO 15189:2014, valid until November 25, 2019).

The research was conducted in accordance with the provisions of GCP (1996), the Convention of the Council of Europe on Human Rights and Biomedicine (1997), the Declaration of Helsinki of the World Medical Association on Ethical Principles for Research Involving Human Subjects (1964–2008), Order of the Ministry of Health of Ukraine No.690 on September 23, 2009 (as amended by Order of the Ministry of Health of Ukraine No.523 on July 12, 2012). Approval of the Bioethics Commission of the Bukovinian State Medical University (Protocol No.2 on February 9, 2015).

Statistical processing of the results was performed using Statistica 13.0 (StatSoft Inc., USA). Statistical values were determined considering standard deviation (S), standard error (m), arithmetic mean of the sample (M), using Shapiro-Wilk test (normal distribution with a sample size greater than 30, $p<0.05$) and Kolgomorov-Smirnov test. The quantitative indicators in samples with normal distribution were evaluated using the Student's t-test, the statistical significance of the results was determined at $p<0.0001$.

The research was carried out within the framework of the research work of the Department of Pediatrics, Neonatology and Perinatal Medicine of BSMU on the topic: "Improvement of prognosis, diagnosis and treatment of perinatal pathology in newborns and infants, optimization of schemes of catamnestic observation and rehabilitation" (State Registration No.0115U002768) and research on the topic: "Chronobiological and adaptive aspects and peculiarities of vegetative regulation in pathological conditions in children of different age groups" (State Registration No.0122U002245).

Results and Discussion

Group 1 consisted of 36 boys (66.67%) and 18 girls (33.33%). Anthropometric characteristics of children at birth were as follows: weight [1105.66± ±128.53] g, body length – [35.36±1.05] cm, head circumference – [26.58±2.06] cm, trunk circumference – [24.86±2.04] cm. Among the newborns of group 2 there were 23 (46.0%) boys and 27 (54.0%) girls with birth weight [2364.00±113.67] g, body length – [45.21±0.75] cm, head circumference – [31.59±0.71] cm, and trunk circumference – [30.51±1.46] cm. In comparison, anthropometric parameters showed significant differences, as they differed according to gestational age at birth – group 2 included children born at 34–36/6 weeks of gestation, which is considered almost full-term. Despite a certain percentage of maternal somatic pathologies and risk factors during pregnancy and childbirth, newborns of this group did not have any adaptation disorders in the neonatal period, so their study results were used as controls for the evaluation of laboratory parameters in children of study group 1.

The analysis of the somatic history of the women in group 1 showed that the birth of children before 32 weeks was observed in the following cases: 66.67% – in repeated pregnancy and childbirth, 42.59% – in age-matched first-time mothers, 66.67% had an emergency cesarean section. Compared with group 2, group 1 mothers were more likely to have somatic pathology, namely cardiovascular system – 43 (79.63%) and 3 (6.0%) cases, respectively, $p<0.0001$; urinary system – 42 (77.78%) and 3 (6.0%) cases, $p<0.0001$; GIS – 26 (48.15%) and 3 (6.0%) cases, $p<0.0001$; endocrine system – 19 (35.19%) and 3 (6.0%) cases, $p=0.0003$; respiratory system – 16 (29.63%) and 4 (8.0%) cases, $p=0.0163$; grade 2–3 anemia was diagnosed in 26 (48.15%) and 3 (6.0%) cases, respectively, $p<0.0001$.

The study of the peculiarities of the obstetrical and gynecological anamnesis of the women of group 1 showed the following: induced and spontaneous abortions, stillbirths, deaths of children under 1 year of age – 22 (40. 74%) cases, while the frequency of this indicator in group 2 was 1 (3.22%), $p<0.0001$; in vitro fertilization – 10 (18.52%) and 1 (3.22%) cases, $p=0.0138$; infertility – 13 (24.07%) and 2 (6.45%) cases, $p=0.0138$; preterm labor – 2 (3.70%) cases in the main group. Gynecological pathology in women was represented by: cervical insufficiency – 20 (37.04%) and 1 (3.22%) cases, $p<0.0001$; vaginitis – 16 (29.36%) and 2 (6.45%) cases, $p=0.0023$; TORCH infections – 18 (33.33%) and 1 (3.22%) cases, $p=0.0001$; uterine developmental abnormalities were detected in 9 (16.67%) cases.

Placental insufficiency during pregnancy was much more common in women of group 1, with fetal growth retardation detected in 29 (53.70%) cases, while in group 2 – only in 1 (3.22%) case, $p<0.0001$; threatened miscarriage and/or preterm delivery – in 16 (29.63%) and 2 (6.45%) cases, respectively, $p=0.0025$. Complications during labor included: fetal distress – 36 (66.67%) and 2 (6.45%) cases, $p<0.0001$; premature rupture of membranes – 18 (33.34%) and 1 (3.22%) cases, $p<0.0001$; abnormal presentation of the fetus – 17 (31.48%) and 1 (3.22%) cases, $p=0. 0002$; premature detachment of a normally located placenta – 13 (24.07%) and 1 (3.22%) cases, $p=0.0023$; ute-

rine bleeding – 11 (23.37%) cases in women of group 1. In addition, in 4 (7.47%) cases in women of group 1, a prenatal death of a twin fetus was diagnosed.

Newborns of group 1 had certain peculiarities of postnatal adaptation, which led to further development of severe pathological conditions in the neonatal period. The Apgar score of children of this group was [4.20±1.11] points at the 1st minute and [5.52±1.12] points at the 5th minute, which was significantly lower in comparison with the indicators of group 2 – [6.85±0.24] points and [7.82±0.35] points, respectively. The severity of the condition of children in group 1 was due to: Asphyxia – 32 (59.26%) cases; respiratory disorders – 54 (100%) cases; primary pulmonary atelectasis – 50 (92.59%) cases; hyaline membrane disease – 38 (70.37%) cases; 4 (7.41%) newborns were diagnosed with congenital pneumonia. Among children of group 1, 18 (33.33%) cases had pronounced signs of morphological and functional immaturity – 19 (35.19%) cases.

According to our data, all children in group 1 had signs of Multiple Organ Disfunction Syndrome (MODS), which included the following lesions: central nervous system and respiratory system – 54 (100.00%) cases each, cardiovascular system – 16 (29.63%) cases, hemorrhagic syndrome – 17 (31.48%) cases, anemic syndrome – 15 (27.78%) cases, disseminated intravascular coagulation – 14 (25.93%) cases. Convulsive syndrome was diagnosed in 15 (27.78%) newborns, 8 (14.81%) children had cerebral edema and/or were diagnosed with cerebral coma. Intraventricular hemorrhage of grade 1, 2, and 3–4 was diagnosed in 8 (14.81%) and 4 (7.41%) neonates, respectively. Signs of periventricular leukomalacia were observed in 8 (14.81%) children of group 1. It should be noted that in 11 (20.37%) cases of newborns of this group ulcerative Non-Specific Enterocolitis (UNEC) of the first degree was diagnosed, in 4 (7.41%) cases – UNEC of the second degree.

All 54 (100.00%) children in the main group showed, along with other symptoms of early neonatal disease, signs of nutritional dysfunction resulting in inadequate enteral absorption of the main components and requiring adequate supplementation by the administration of Parenteral Nutrition (PN). According to the literature, the disruption of the feeding schedule is usually caused by the child's inability to achieve complete enteral nutrition within the specified time, which is manifested either by a decrease in the number of feedings or their interruption due to the appearance of signs of malnutrition during feeding. Because the presence of nutritional dysfunction is easier to diagnose with an established feeding schedule, some studies have used the time to achieve total Enteral Nutrition (EN) or the need to interrupt EN with the addition of formula as criteria for assessing PN [9; 10]. A multicenter randomized trial published in 2002 concluded that the color of gastric residue in preterm infants does not always confirm PN [11]. The 2015 Canadian Guidelines for the Feeding of Very Low Birth Weight (LBW) Infants state that the yellow or green color of gastric residual volume alone cannot be used as a guide to diagnose LBW and also note that the use of abdominal circumference measurements to diagnose LBW is not recommended. [12] According to recent published scientific data, food intolerance in PB is usually manifested by an increase in Residual Gastric Volume (RGV) greater than 50% of previous feeding volume, accompanied by vomiting and/or bloating, and blood in stool [4].

Considering the purpose of the planned research, we raised the question of determining the clinical signs of ND in PB more broadly. Considering the expediency of generalizing the main diagnostic criteria characterizing the combined nature of the formation of Functional Gastrointestinal Disorders (FGID), we analyzed the probable clinical and paraclinical signs of dysfunction of the hepatobiliary system, pancreas and intestine in severe forms of perinatal pathology in this category of newborns.

The findings showed that the signs of ND in PB of less than 32 weeks gestational age were: residual stomach volume of more than 50% – in all 54 (100.00%) children; regurgitation and/or vomiting – in 32 (59.26%) cases; increased liver size and/or hepatolienal syndrome – in 54 (100.00%) and 43 (79.63%) cases, respectively, in neonates of the main and comparison groups; 48 (88.89%) children of group 1 had intestinal flatulence, 28 (51.85%) cases had blood in stool and 8 (14.81%) cases had acholic stool; 50 (92.59%) children had jaundice; 48 (88.89%) newborns had edema; 45 (83.33%) newborns had signs of endotoxemia.

The results of biochemical blood tests in the main group of PBIs showed significant homeostasis disorders. The data obtained, considered the indicators in the comparison groups, are presented in *Table 1*.

The analysis of the biochemical spectrum of blood serum revealed deviations of indicators, which, to a certain extent, allow to determine the

Table 1. Biochemical parameters of newborn blood serum (M±m)

Parameter	Group 1 (n=54)	Group 2 (n=50)
Total Protein, g/l	50.44±2.60*	55.20±2.34
Total bilirubin, μmol/l	131.92±6.50*	79.94±3.98
Direct bilirubin, μmol/l	2.33±0.11	–
Indirect bilirubin, μmol/l	129.59±4.70*	79.94±3.98
Alanine Aminotransferase, U/l	17.22±0.84*	10.26±0.44
Aspartate Aminotransferase, U/l	48.00±2.33*	38.41±1.76
Lactate Dehydrogenase, U/l	1185.12±91.6*	776.9±29.39
Alkaline Phosphatase, U/l	361.40±12.38*	346.6±19.79
Gamma-glutamyl Transferase, U/l	127.82±8.47*	108.9±9.87
Cholesterol, mmol/L	3.54±0.37*	2.21±0.15
Triglycerides, mmol/L	0.57±0.06*	0.72±0.05
Glucose, mmol/L	2.41±0.12*	3.34±0.15
Urea, mmol/L	3.85±0.16*	3.45±0.17
Creatinine, μmol/l	79,93±3,89*	60.32±2.63
Amylase, U/l	5.34±0.29*	25.0±0.23
Lipase, U/l	12.46±0.63*	21.5±0.21
Trypsin, μg/l	235.43±11.77*	427.4±11.15
Leucine Aminopeptidase, U/l	27.15±1.36*	39.96±0.27

Note: * – significant difference between the comparison groups ($p<0.0001$).

main pathophysiological principles of food intolerance in severe forms of perinatal pathology. A significant decrease in the level of total protein was noted, which indicates a lack of protein-synthesizing function of the liver and may cause the development of hypoproteinemic and hemorrhagic syndromes. The consequence of hypoproteinemic syndrome, due to the decrease in albumin content, is decreased plasma oncotic pressure, which can cause edema syndrome. Hemorrhagic syndrome develops in newborns as a result of insufficient synthesis of proteins that are blood coagulation factors (fibrinogen, prothrombin, proconvertin, and proaccelerin) [13]. High levels of urea and creatinine are characteristics of disorders of protein metabolism, as the main source of nitrogen from amino acids and their degradation products, as well as urea-forming function of the liver and renal excretory function. The results of the PB examination also showed an increased level of cholesterol in the blood serum, which is a manifestation of hepatocyte cytolysis and is due to the activation of lipid peroxidation in the absence of an antioxidant defense system [14]. The data analysis also showed an increased level of total bilirubin, mainly due to the indirect fraction, which is associated with increased hemolysis due to postnatal physiological processes of the red blood cell, as well as pathological processes, in particular bilirubin metabolic disorders and cholestasis. A decrease in triglyceride levels indicates immature lipid metabolism in the PBI body and inadequate intestinal absorption. According to the literature, a decrease in this indicator is also associated with inadequate or absent enteral nutrition. Decreased glucose levels in neonates are associated with impaired gluconeogenesis in the liver and may be due to inadequate intake. The increase in ALP activity is explained by the activation of glucose release from tissues after dephosphorylation [15; 16].

High levels of AlAT and AsAT activity indicate activation of cytolytic processes in neonatal liver under hypoxia. The function of AlAT and AsAT is also related to the transamination process, which plays a key role in intermediate metabolism, ensuring the synthesis and breakdown of amino acids such as glutamic acid, aspartic acid and alanine. When converted to keto acids, which are components of the tricarboxylic acid cycle, they become a source of energy in the body. A significant increase in AlAT and AsAT in the acute period of hypoxic injury can also be explained by certain compensatory mechanisms aimed at providing cells with energy in the form of ATP, the formation of important biochemical molecules – acetyl CoA, NAD, FAD [17].

The results of the research also showed an increase in the enzymatic activity of GGT, which indicates both an increase in the activity of the glutathione system and glutathione-dependent enzymes, and the activation of cytolytic processes in the liver. An increase in LDH, which ensures the integration of carbohydrate and lipid metabolism, in children of the main group indicates a dysregulation of anabolism and catabolism, anaerobic and aerobic glycolysis [14]. Taking into account the main pathophysiological mechanisms of formation of HS dysfunction, the complex of signs of ND in PBI includes cytolysis syndrome (increased enzymatic activity of AlAT, AsAT and LDH), cholestasis syndrome (increased activity of GGT and ALT, cholesterol and bilirubin levels) and hepatocellular failure syndrome (decreased total protein and increased cholesterol levels).

The study of the indicators of the functional state of the pancreas showed a significant decrease in enzymatic activity, which confirms the insufficiency of its exocrine function in the presence of signs of ND in the PBI. A review of the current literature shows an insufficient number of scientific studies on exocrine insufficiency of the pancreas both in the general population and in patients with various diseases that lead to impaired functional state of the pancreas. However, it should be noted that the interest of researchers in this problem has increased in recent years. It is believed that exocrine insufficiency of the pancreas should be considered not as a dysfunction of a single organ, but as a general syndrome of digestive disorders. Accordingly, the aspects of diagnosis and treatment should include a more holistic approach [18; 19].

The study of laboratory markers of intestinal ND was performed with the determination of A1AT, FE-1, PMN-elastase, albumin and FC in the coprofiltrate of newborns. The results are presented in *Table 2*.

Analysis of the results showed significant differences in coprofiltrate indices in newborns of the main group under conditions of hypoxic damage to the body. In particular, signs of inflammation of the intestinal mucosa are confirmed by high levels of calprotectin. It is assumed that the increase of this indicator is due to its release from activated neutrophils. In the feces, it reflects the transepithelial migration of granulocytes into the intestinal lumen, confirming the inflammatory rather than functional nature of the disease [20]. Increased permeability of the intestinal mucosa due to inflammatory exudation from the altered epithelium also leads to protein loss and impaired parietal absorption. This may result in increased translocation of endotoxins and opportunistic pathogens from the intestinal lumen into the general circulation. The results obtained also showed a decrease in PMN-elastase, which is secreted by granulocytes and regulates inflammatory and immune responses, in the coprofiltrate of newborns. The decrease indicates the insufficiency of this compound in the regulation of intestinal anti-inflammatory mechanisms in PBI. References also suggest the possibility of cholestasis in severe forms of hypoxic inflammation [21–23]. A1AT, which is considered an acute-phase protein and a primary inhibitor of serine proteases in inflammation, was significantly elevated in group I neonates. According to the literature, A1AT is synthesized mainly by liver endoplasmic reticulum, polymorphonuclear neutrophils, alveolar macrophages, enterocytes, monocytes and Paneth cells. A1AT is an antiprotease that neutralizes excess proteases, inhibits chemotaxis and neutrophil adhesion. It is able to inhibit the release of proinflammatory interleukins, scavenge reactive oxygen species, and thus activate the body's anti-inflammatory response [24; 25]. Newborns in group 1 had slightly higher levels of FE-1, but the difference was not significant. Analysis of the literature

Table 2. Comparative characteristics of the biomarkers of the coprofiltrate in the newborns of the comparison groups (M±m)

Parameter	Group 1 (n=54)	Group 2 (n=50)
Calprotectin, µg/g	392.47±19.63*	64.74±3.11
Albumin, µg/g	39.24±2.94*	11.28±0.90
PMN - Elastase, ng/g	89.32±4.49*	257.53±17.30
α-1-Antitrypsin, µg/g	358.42±2.89*	241.15±18.90
Fecal Elastase-1, µg/g	289.58±14.49*	246.98±16.79

Note: * – significant difference between the comparison groups ($p<0.0001$).

shows that the increase in the level of FE-1 can usually be earlier than that of other enzymes, especially in the subclinical stage of hypoxic inflammation [23]. In our opinion, the absence of a significant difference between the indices of the comparison groups may indicate the imperfection of this mechanism in PBI under conditions of significant immaturity of the organism.

Thus, in view of the obtained data, it can be concluded that ND in premature infants is caused by combined disorders of the functional state of the hepatobiliary system, pancreas and intestine. The pathophysiological mechanisms are based on hypoxic inflammation of the body, which has a negative impact on the formation of compensatory mechanisms, starting from the subcellular level of disorders. Detection of these changes, starting from the biochemical level, will improve the diagnosis of gastrointestinal disorders to prevent the development of severe dysfunction in the acute period of neonatal diseases, prevent the development of functional and chronic pathology in the later years of life.

Conclusions

1. Disturbances of the functional state of the gastrointestinal system in premature infants are caused by combined dysfunction of the hepatobiliary system, pancreas and intestine against the background of hypoxic damage and morphological and functional immaturity of the body.

2. Clinical signs of nutritional deficiency in newborns, taking into account the frequency of cases, include: residual volume of more than [50.00–100.00]%; regurgitation and/or vomiting – 59.26%; increased liver size (100%) and/or hepatolienal syndrome – 79.63%; flatulence – 88.89%, blood in coprofiltrate – 51.85%; acholic stools – 14.81%; jaundice – 92.59%; edema – 88.89%; endotoxemia – 83.33%.

3. The pathophysiologically substantiated biochemical markers of gastrointestinal disorders in premature infants are from the hepatobiliary system include increased activity of AlAT, AsAT and LDH (cytolysis syndrome); increased activity of GGT and ALP, cholesterol and bilirubin levels (cholestasis syndrome); decreased level of total protein and increased level of cholesterol (cholestasis syndrome and hepatic cell failure syndrome). Insufficiency of external secretory function of pancreas manifests by decreased level of amylase, lipase, trypsin and leucine aminopeptidase; inflammation and increased permeability of the intestinal mucosa (increased levels of calprotectin, albumin, alpha-1-antitrypsin, fecal elastase-1; decreased PMN elastase).

Prospects for further research are the comparison of clinical and laboratory parameters characterizing HBS dysfunction in PBI with regard to gestational age at birth.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations rele-vant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

Funding Sources

There are no external sources of funding.

Consent for publication

All authors give their consent to publication.

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Received: 26 Oct 2024
Accepted: 31 Dec 2024
Published: 31 Dec 2024

Cite in Vancouver style as: Godovanets OS, Nechytailo YuM. The study of gastrointestinal distress markers in children of gestational age less than 32 weeks with pathological conditions of the newborn period. Inter Collegas. 2024;11(4):26-34. https://doi.org/10.35339/ic.11.4.gon

Archived: https://doi.org/10.5281/zenodo.15170574

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THE STATE OF LOCAL HUMORAL IMMUNITY OF THE ORAL CAVITY IN CHILDREN FROM DIFFERENT REGIONS OF BUKOVINA

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https://doi.org/10.35339/ic.11.4.gok

ABSTRACT

Background. Saliva is an important protective factor in the oral cavity that maintains dental health, promotes enamel demineralization, reduces enamel demineralization and provides local humoral protection. Important components of this environment are lysozyme and secretory immunoglobulin A. Their levels depend on individual characteristics, hygiene and nutrition and make it an important marker for assessing the risk of caries.

Aim. To investigate the state of local humoral immunity of the oral cavity in children by determining the levels of lysozyme and sIgA in the oral fluid.

Materials and Methods. To achieve this goal, we examined 215 children aged 6 years living in Bukovyna. We divided them into observation groups depending on the region of residence and the level of caries intensity. The state of local immunity of the oral cavity was determined by the levels of sIgA and lysozyme in the oral fluid. The degree of reliability of the results was statistically assessed.

Results. As a result of immunological studies, it was found that under conditions of varying intensity of carious lesions there is a steady tendency to decrease the concentration of lysozyme in the oral fluid of children. The results are the lowest in children from Vyzhnytsia district. In children of Dniestr district, lysozyme activity is 7.32% higher, and in children of Chernivtsi district – by 15.35% ($p<0.05$). The content of sIgA in children of the Vyzhnytsia district was (0.29±0.002) μg/l, which was 6.45% and 12.12% lower than the values of children of the Dniester and Chernivtsi districts ($p<0.05$). A decrease in its concentration in the oral fluid correlates with an unfavourable prognosis of the disease.

Conclusions. Thus, we found that in children with carious lesions there were changes in the system of nonspecific humoral immunity of the oral cavity.

Keywords: *children, caries, saliva, lysozyme, immunoglobulin.*

Introduction

Saliva is an important protective factor of the oral cavity, which maintains dental health, promotes enamel demineralization, reduces its demineralization and provides local humoral protection [1]. Important components of this environment are lysozyme and secretory immunoglobulin A (sIgA) [2].

Lysozyme destroys bacterial cell walls through enzymatic activity and has a bactericidal effect independently. It creates pores in the bacterial membranes, which leads to their osmotic death and increases the permeability of cells to other antimicrobial molecules [3–5]. These properties make it possible to effectively destroy bacterial biofilms that protect pathogens from the effects of antibacterial drugs. Even with modification of the peptidoglycan structure or loss of the cell wall, bacteria retain sensitivity to the cationic mechanisms of lysozyme. The activity of this enzyme in the oral fluid correlates with the state of local immunity and indicators of antimicrobial protection of the oral cavity.

Secretory immunoglobulin A (sIgA) prevents the adhesion of pathogenic bacteria, such as Streptococcus mutans, to tooth enamel. Decreased levels of sIgA are observed in children with carious tooth lesions and are associated with an increase in the number of cariogenic microorganisms. The level of sIgA depends on individual characteris-

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tics, hygiene and nutrition, which makes it an important marker for assessing the risk of caries [4–7].

Monitoring of lysozyme and sIgA allows to effectively assess the state of oral immunity, which determines the relevance of this study.

The **aim** of the study was to investigate the state of local humoral immunity of the oral cavity in children by determining the levels of lysozyme and sIgA in the oral fluid.

Materials and Methods

To achieve this goal, we examined 215 children aged 6 years living in Bukovyna. We divided them into observation groups depending on the region of residence and the level of caries intensity.

The state of local oral immunity was determined by the levels of sIgA and lysozyme in the oral fluid. The studies were conducted at the Educational and Research Laboratory of Bukovinian State Medical University.

Unstimulated oral fluid was collected on an empty stomach by spitting into test tubes. After that, it was centrifuged at 3000 rpm for 15 minutes and the supernatant was collected, which was stored in a freezer at –20°C until the reaction was performed.

The concentration of sIgA was determined using the simple radial diffusion method in agar according to G. Manchini. The content of lysozyme in oral fluid samples was determined using the method of Gorin G. in the modification of Levitsky A.P. and Zhigina O.O.

The degree of reliability of the results obtained was statistically assessed in the case of normal distribution of both samples by the Student-Fisher test, in other cases – by the Wilcoxon U test for independent samples and the Wilcoxon T test for dependent samples.

Results and Discussion

As a result of immunological studies, it was found that under conditions of different intensity of caries lesions there is a steady tendency to decrease the concentration of lysozyme in the oral fluid of children: from (34.90±1.71) units/l – under conditions of low, to (30.05±1.68) units/l – under conditions of high intensity, ($p<0.05$) (*Fig. 1*).

Children in the Vyzhnytsia district have the lowest results. In children of Dniestr district, lysozyme activity is 7.32% higher, and in children of Chernivtsi district – 15.35% ($p<0.05$). We believe that such results are associated with a decrease in the function of the specific protective barrier of the oral cavity, which protects the macroorganism from the damaging effects of pathogenic and opportunistic microorganisms. The content of sIgA in children of the Vyzhnytsia district was (0.29± ±0.002) μg/l, which was 6.45% and 12.12% lower than the values of children of the Dniester and Chernivtsi districts ($p<0.05$) (*Fig. 2*).

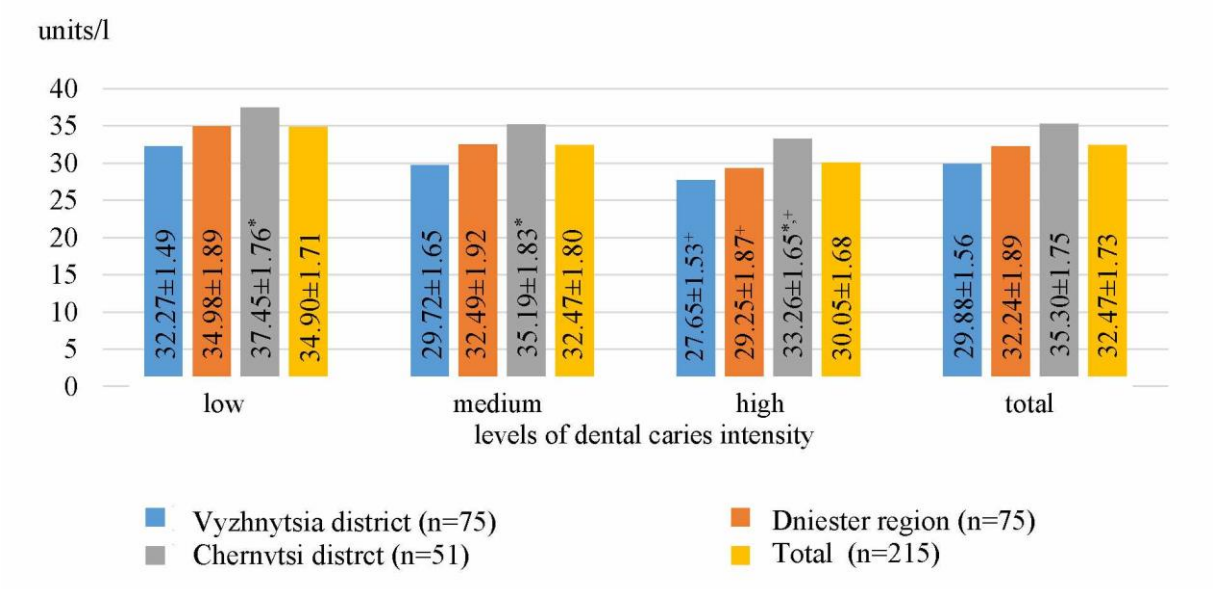

Fig. 1. Lysozyme levels in the oral fluid of children living in Bukovyna (M±m)

Notes: * – difference between the values of children from Vyzhnytsia and Dniester, Chernivtsi districts is significant ($p<0.05$);

** – difference between the values of children from Dniester and Chernivtsi districts is significant ($p<0.05$);

+ – difference between children with low and medium, high levels of dental caries intensity, significant ($p<0.05$);

++ – difference between children with medium and high levels of dental caries intensity, significant ($p<0.05$).

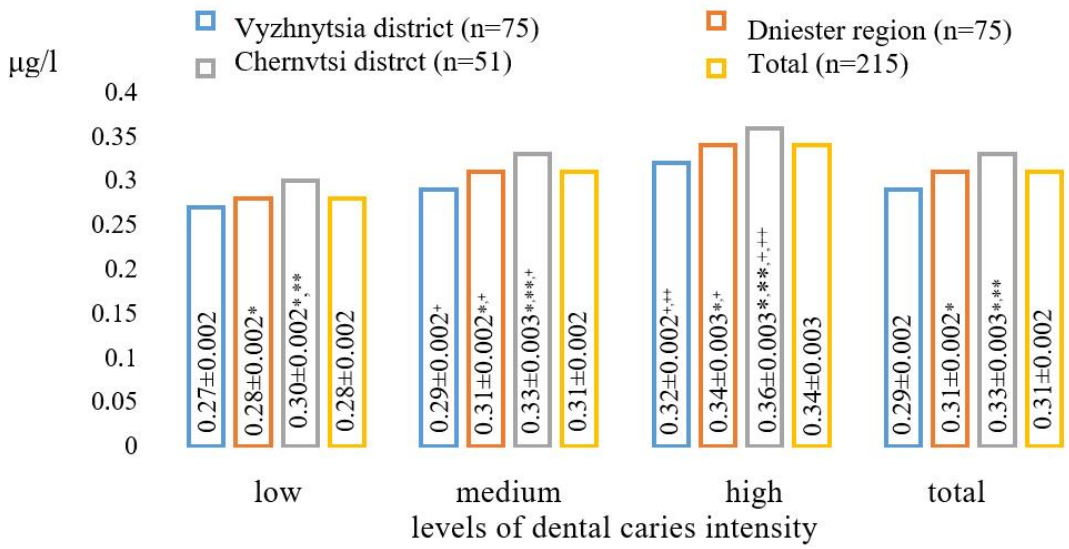

Fig. 2. Levels of sIgA in the oral fluid of children living in Bukovyna (M±m)

Notes: * – difference between the values of children from Vyzhnytsia and Dniester, Chernivtsi districts is significant ($p<0.05$);

** – difference between the values of children from Dniester and Chernivtsi districts is significant ($p<0.05$);

+ – difference between children with low and medium, high levels of dental caries intensity, significant ($p<0.05$);

++ – difference between children with medium and high levels of dental caries intensity, significant ($p<0.05$).

A decrease in its concentration in the oral fluid correlates with an unfavourable prognosis of the disease: the highest level of sIgA in the oral fluid was determined at high caries intensity and ranged from (0.32±0.002) to (0.36±0.003) µg/l ($p<0.05$). At medium and high levels of caries intensity, a significant decrease in the content of sIgA in the oral fluid of children was observed, which is due to the insufficiency of the function of nonspecific humoral defence at the local level.

Conclusions

Thus, we found that in children with carious lesions there were changes in the system of nonspecific humoral immunity of the oral cavity. The indicators were probably worse in conditions of high intensity of caries, which correlated with the condition of the hard tissues of the teeth. Imbalance in the humoral immunity system and a decrease in the local protective capabilities of the oral cavity create suitable conditions for the development or aggravation of a cariogenic situation.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

Funding Sources

There are no external sources of funding.

Consent for publication

All authors give their consent to publication.

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Received: 25 Oct 2024
Accepted: 31 Dec 2024
Published: 31 Dec 2024

Cite in Vancouver style as: Godovanets OI, Kotelban AV. The state of local humoral immunity of the oral cavity in children from different regions of Bukovina. Inter Collegas. 2024;11(4):35-8. https://doi.org/10.35339/ic.11.4.gok

Archived: https://doi.org/10.5281/zenodo.15170737

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ANALYTICAL STUDY OF THE LEADING CAUSES OF DEATH OF PALLIATIVE PATIENTS

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https://doi.org/10.35339/ic.11.4.smh

ABSTRACT

Background. Palliative and Hospice Care (PHC) aims to prevent premature death of patients from complications of serious illnesses and their comorbid impact on vital functions. As well as adequate pain relief, treatment should be aimed at alleviating suffering and improving the quality of life of such patients. The causes of death of palliative patients, which are closely related to the PHC organization, in particular to the package budget financing of inpatient and mobile palliative care for adults and children, the leading needs of palliative patients, remain insufficiently studied.

Aim. Analysis of the main causes of death of palliative patients depending on the diagnosis and determination of their impact on the organization of palliative and hospice care.

Materials and Methods. The method of system analysis, comparative method and bibliosemantic method were used for the research.

Results and Conclusions. Causes of death were studied for diseases listed as palliative in severe cases and in the presence of complications. The analysis allows us to deepen our understanding of the practical aspects of organizing palliative and hospice care in meeting the needs of palliative patients, adults and children. The summary of the causes of death allows us to group these causes into organ and system failure; vascular crises; asphyxia; thromboembolic conditions; infectious complications up to sepsis; chronic intoxication; tumor growth in other organs with disruption of their vital functions, metastasis; malignancy of benign tumors; complications of treatment; brain and spinal cord lesions due to epileptic seizures, injuries, inflammatory processes; endocrine comas; gangrene and bedsores; severe immunodeficiency; underdevelopment or absence of organs in congenital malformations; prematurity; suicides in depressive states.

Keywords: *palliative and hospice care, primary palliative diagnosis, comorbidity*.

Introduction

Palliative and Hospice Care (PHC) is provided to terminally ill patients in the last days of their lives and is intended to reduce their suffering, the feeling of pain and to prepare for a dignified death. Modern development of medical technologies theoretically allows to ensure painless dying, which is possible with the correct organization of medical care. The countries with developed PHC systems offer patients recognition of their palliative status, stay in specialized institutions (hospices, palliative departments and wards) or in "hospices at home", adequate pain relief, euthanasia as an option, as well as social support and spiritual support, which extend to both the patient himself and his loved ones (caregivers) [1–3].

A significant part of palliative diseases belongs to the category of disabling and is accompanied by chronic intense pain [4; 5]. Depending on the main palliative diagnosis and comorbid pathology, in severe palliative conditions, nociceptive (associated with nerve irritation), neuropathic (associated with organic nerve damage) type of pain prevails, or a combination of these types of pain is present. Depending on the intensity of pain, which is derived from the characteristics of the pathological process and individual perception of pain, narcotic drugs (morphine, oxycodone, buprenorphine, etc.), non-narcotic drugs (primarily Nonsteroidal Anti-Inflammatory Drugs, NSAIDs) and adjuvants (not intended for direct pain relief, but capable of enhancing the effect of analgesic drugs – sedatives, hypnotics, anticonvulsants, neuroleptics, etc.)

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are used for pain relief [2; 6; 7]. The recent legalization of medical cannabis theoretically significantly expands the possibilities of adequate pain relief. However, to practically realize this opportunity, Ukraine needs to accelerate the adoption of by-laws regulating cultivation of cannabis, production of cannabis-based drugs, and simplify the procedures for obtaining these drugs by palliative patients [8; 9].

Pain in severe palliative conditions is not a "signal" pain, i.e., it does not indicate a previously unknown health problem. On the contrary, it is emotionally debilitating and depletes the immune and endocrine systems. Its impact on inflammatory processes is negative due to its participation in "pathological circles" [2; 4; 5; 10]. This indicates the need for constant adequate pain relief for palliative patients, but taking into account the risks of excessive sedation, which can lead to death. It is these risks that allow us to talk about the need to prevent premature death in patients who already expect it to be imminent. In the ongoing debate about the risks and benefits of long-term pain relief with narcotic drugs, it is necessary to focus on evidence collected according to the rules of evidence-based medicine [11; 12].

In recent years, researchers from the Ukrainian Center for Public Data (Kyiv, Ukraine) and Kharkiv National Medical University have made progress in determining the list of palliative diseases in Ukraine [13–16]. Representatives of the first organization calculated the need for PHC and determined the list of main palliative diagnoses of adults and children for 2018. Representatives of the second organization expanded this list, calculated the need for PHC for 2019–2020 and forecasted this need for 2021–2022. Subsequently, this forecast was checked and revised retrospectively using the creeping trend method with a constant smoothing segment. The method itself was also improved [16; 17].

In their further studies, representatives of the Kharkiv group studied the features of the organization of PHC at the regional level [18; 19], improved the questionnaire on the quality of life of palliative patients of neurological and oncological profiles [20; 21], studied the issues of types of pain in different palliative diagnoses, features of pain relief [4; 6; 7], attitudes towards the possibility of legalizing euthanasia [22–25]. To date, the causes of death of palliative patients, which are closely related to the organization of PHC, in particular, with the package budget financing of stationary and mobile palliative care for adults and children [26], and the leading needs of palliative patients [1; 8], remain insufficiently studied in the works of the authors and according to the results of searches on PubMed, Google and Google Scholar.

The **aim** of the study was to analyze the main causes of death of palliative patients depending on the diagnosis and to determine their impact on the organization of palliative and hospice care.

Materials and Methods

The research used methods of systematic analysis, comparative and bibliosemantic, with a search for sources on PubMed, Google and Google Scholar using the keywords "palliative and hospice care", "causes of death of palliative patients", "comorbidity of palliative diseases" in Ukrainian and English. In connection with the theoretical approach to the research, bioethical examinations of the research materials were not conducted. Statistical methods were also not used.

Results and Discussion

The causes of death of cancer patients (C00–C97, D00–D48 according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, ICD-10) are cancer intoxication, failure of affected organs and systems (respiratory, cardiovascular, renal, hepatic failure), cachexia, metastasis and germination of tumors to other organs with disruption of their vital functions, thromboembolism, infectious complications (sepsis, infection of decaying tumors). Treatment complications are also possible. For example, death due to excessive sedation with narcotic analgesics [7; 27; 28]. Cancer patients with malignant neoplasms accounted for (36.3–40.4)% of all palliative adult patients and (13.5–17.8)% of children with palliative diagnoses in Ukraine for the period 2018–2020, according to the calculation of the need for PHC in Ukraine performed by Nesterenko V.G. et al. (2021) [14–17].

The causes of death from cardiovascular diseases (I00–I99 according to ICD-10) are usually acute and chronic heart failure, circulatory failure due to myocardial infarction and stroke of the brain vessels (hemorrhagic and ischemic), chronic heart failure, thromboembolic conditions and cardiac arrhythmias. Rupture of aneurysms against a background of hypertension with internal bleeding is also possible [29–33]. Cardiovascular diseases accounted for (32.8–40.1) % of all palliative adult patients and (1.6–2.3) % of children with palliative diagnoses in Ukraine for the period 2018–2020 according to the calculation of the need for PHC in Ukraine.

The causes of death in adult dementia (F72–F79 according to ICD-10) and severe and profound mental retardation in children (F00–F03 according to ICD-10) are swallowing disorders and related asphyxia and aspiration pneumonia; urinary tract infections up to septic conditions; pressure ulcers and their infectious complications; anorexia; treatment complications [34–37]. An important aspect of organizing PHC for these categories of palliative patients is the resumption of the collection of statistical data on morbidity, which was discontinued in Ukraine in 2019.

The causes of death from tuberculosis (A15–A19 according to ICD-10) are bronchial obstruction and respiratory failure; massive pulmonary hemorrhage; HIV infection (in combination with tuberculosis, the stage of this disease is defined as AIDS); meningitis. The infectious process threatens the life of the patient when infected with a pathogen with multidrug resistance to antibiotics [38–41]. In 2022, tuberculosis was the second leading cause of death from infectious diseases in the world, second only to COVID-19 (7.5 million new cases of infection). In 2023, it was in first place (8.2 million new cases of infection). At the same time, the elderly and people with disabilities are at risk and often require palliative care [42–45].

The causes of death in diabetes mellitus (E10–E14 according to ICD-10) are diabetic coma, vascular crises, renal failure, infectious complications (up to sepsis) due to the development of gangrene of the lower extremities, and pressure sores [46].

The causes of death in rheumatoid arthritis (M05–M06 according to ICD-10) are mainly infectious complications (up to sepsis) of immobility caused by the disease (bedsores, pneumonia) and complications of treatment (primarily immunosuppressants, which reduce the body's resistance to infectious diseases and can cause liver fibrosis) [47–49]. Fibrosis and cirrhosis of the liver (K74 according to ICD-10) are also considered as palliative conditions in adults and children. Most often, their occurrence is associated with chronic hepatitis (K73, K75.2, K75.3 according to ICD-10), and death is caused by liver failure, bleeding, malignancy (liver cancer), infectious complications of immobility in these diseases (skin infections, pneumonia), which can cause sepsis [50].

The causes of death in HIV infection are the development of the final stage of the disease (AIDS) and related infectious and oncological processes (B20–B24 according to ICD-10). Due to the ineffectiveness of immune defense, even opportunistic infections can cause severe consequences, and the range of possible oncological diagnoses is significantly expanded (for example, due to Kaposi's sarcoma). NeuroAIDS can also be a direct cause of death. In war conditions, temporarily displaced persons and migrants with HIV-positive status may be deprived of access to antiretroviral therapy, which can accelerate the development of AIDS and its fatal complications [51–53].

The causes of death in Chronic Obstructive Pulmonary Disease (COPD) (J43–J47 according to ICD-10) are respiratory failure due to pneumonia, bronchial obstruction, destruction of lung tissue affected by the infectious process, and tumor destruction. Treatment complications are also possible: allergic reactions up to anaphylaxis, cardiac arrhythmias, thromboembolism, steroid insufficiency due to long-term treatment with inhaled corticosteroids. Chronic lack of oxygen can cause heart failure. The onset of death is significantly accelerated by the widespread use of tobacco smoking in the world [54–57]. Even before the start of the COVID-19 pandemic, COPD was one of the leading causes of death in the world. Thus, in 2016, the disease caused more than 3 million deaths and took 3rd place among the 10 leading causes of death [56]. When collecting data on causes of death, COPD should be counted separately from deaths caused by COVID-19. But in practice, these causes were often not separated.

The causes of death in kidney diseases (N00–N15, N20–N23 according to ICD-10) are renal failure, uremia, infectious complications of inflammatory processes in the kidneys. Severe complications of treatment are also possible: the development of an infectious process at the site of access to the vessels during dialysis, malignancy of kidney tumors during dialysis, gastrointestinal bleeding from damage to the mucous membranes by oral drugs, cardiac arrhythmias due to deviations from the norm of potassium content in the blood caused by treatment with loop and thiazide diuretics, angiotensin-converting enzyme inhibitors [58–63].

The causes of death in cystic fibrosis (E84 according to ICD-10) are respiratory, cardiovascular and hepatic failure, cystic fibrosis of the pancreas and infectious complications of the disease, up to sepsis [64; 65]. Insufficiency of organs and organ systems is also a cause of death in children with mucopolysaccharidosis (E76 according to ICD-10), but in addition to cardiovascular, respiratory and hepatic failure, renal failure should be added.

Other causes of death are seizures that damage the brain, arrhythmias and infectious complications [66; 67].

The causes of death in congenital malformations of newborns (Q00–Q99 according to ICD-10) are the absence or underdevelopment of organs, causing all possible types of organ failure, immediately after birth or during the growth and development of the child. Malformations that are present in the nervous system can cause seizures and paralysis. Complications of surgical treatment of these patients can also affect vital signs [68–71].

Perinatal conditions that lead to death and require palliative care for children (P05–P96 according to ICD-10) may be associated with congenital malformations [72], prematurity, pathology of pregnant women (including extragenital), fetal asphyxia, bleeding of pregnant women and women in labor, infections of pregnant women, fetus and newborn [73–75].

The causes of death in cerebral palsy (G80 according to ICD-10) may include decompensation of the underlying disease with impaired nervous regulation of the respiratory process and the development of acute heart failure, aspiration pneumonia, thromboembolic conditions, seizures, tumor malignancy, infectious processes of the urinary system up to sepsis [76–78].

Inflammatory diseases of the Central Nervous System (CNS) (E70.0 according to ICD-10) lead to death due to depression of the respiratory center, additional damage to nerve structures during epileptic seizures, as well as suicides in a state of depression, malignancy of tumors and complications of treatment [79–81]. In turn, epilepsy (G40 according to ICD-10) can cause Sudden Unexpected Death in Epilepsy (SUDEP) due to damage to nerve centers during an attack with a stroke, trauma (especially when falling during an attack). Drowning during an attack and suicide in depressive states are also possible [82; 83].

Multiple sclerosis (G35 according to ICD-10) can cause death due to the development of pneumonia, vascular crises, pulmonary embolism, infectious complications of immobility (bedsores, urinary tract infections), up to sepsis, and suicide in depressive states [84–87].

The medical and social component of preventing most premature deaths of palliative patients consists of promoting timely examination and treatment of diseases with controllable and conditionally controllable risk factors, promoting vaccinations, safe sex, quitting tobacco smoking, recreational drug use and alcohol abuse, implementing anti-epidemic rules, and building partnerships between patients and doctors in health care [88–93].

Conclusions

The causes of death have been studied for diseases listed as palliative in severe cases and in the presence of complications. The analysis allows us to deepen our understanding of the practical aspects of organizing palliative and hospice care in terms of meeting the needs of palliative patients, adults and children. The summary of determining the causes of death allows us to group these causes into organ and system failure (cardiovascular, respiratory, hepatic and renal); vascular crises (cerebral strokes and myocardial infarctions, cardiac arrest due to rhythm disturbances); asphyxia (fetal, adults due to food aspiration, bronchial obstruction); thromboembolic conditions (including pulmonary embolism); infectious complications up to sepsis, chronic intoxication (cancerous, including during tumor decay; uremia; against the background of multi-resistance of microflora to antibiotics); tumor growth in other organs with disruption of their vital functions, metastasis; malignancy of benign tumors; complications of treatment (including excessive sedation, which caused premature death; electrolyte imbalance; anaphylaxis of unsuccessful surgical interventions and resuscitation); brain and spinal cord lesions due to epileptic seizures, injuries, inflammatory processes; endocrine comas; gangrene and bedsores; severe immunodeficiency; underdevelopment or absence of organs in congenital malformations; prematurity; suicides in depressive states.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations rele-vant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

Funding Sources

There are no external sources of funding.

Consent for publication

All authors give their consent to publication.

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Received: 22 Oct 2024
Accepted: 31 Dec 2024

Cite in Vancouver style as: Smiianov VA, Hubert-Lutecka A. Analytical study of the leading causes of death of palliative patients. Inter Collegas. 2024;11(4):39-48. https://doi.org/10.35339/ic.11.4.smh

Archived: https://doi.org/10.5281/zenodo.15170837

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ETHICS OF VALEOLOGICAL RESEARCH IN HIGHER EDUCATION INSTITUTIONS

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https://doi.org/10.35339/ic.11.4.ssl

ABSTRACT

Background. Teaching valeological disciplines in non-medical higher education institutions is carried out by teachers with pedagogical education, medical education and medical practice (certified physicians). To successfully form valeological (health-saving) competence, the teacher needs to interview non-medical students not only regarding knowledge and practical skills in solving situational tasks using academic tests, but also to study his behavior models, for which special questionnaires with questions on sensitive topics have been developed.

Aim. To develop an algorithm for reliable storage of confidential information regarding the health and behavior of non-medical students studying valeological disciplines.

Materials and Methods. The research was conducted using the sociological method and the system analysis method.

Results and Conclusions. The openness of answers to sensitive questions is ensured only by the confidential storage of the received questionnaire data. For confidential data storage, paper tests-questionnaires should be divided into three parts: a non-confidential test (contains the personal data of the education seeker), a confidential questionnaire (contains an encryption code instead of the personal data of the education seeker), and a code key (contains the code and personal data of students for their identification if necessary to combine the test and questionnaire data). The forced transition to distance learning accelerated the transition to electronic testing-questionnaires and the digitization of paper test-questionnaire data. For confidential questionnaire data storage, encryption of the students' personal data and separation of access to confidential and non-confidential data using standard scripts of the Google Forms, which allows using confidential questionnaires instead of anonymous ones. For scientific purposes, the questionnaire data is statistically processed as anonymous. If necessary, use standard scripts allows decoding the key data and identifying the students.

Keywords: *valeological competence, trusted doctor, "Health Pedagogy", "Fundamentals of Medical Knowledge and Health-Saving", confidential surveys*.

Introduction

The formation of valeological competence consists in the maintaining a healthy lifestyle, changing forms of behavior to safer ones, and the ability to provide effective emergency pre-medical care to save life in critical conditions and during resuscitation [1]. In modern valeological research, valeological competence is considered as the basis for confronting negative genetic, environmental, and behavioral risk factors for diseases and for the fastest recovery after them [2]. Teaching valeological disciplines is an important part of the preventive work of the general public health system of Ukraine. The most qualified teachers of valeological disciplines are medical workers with medical and pedagogical education and medical practice [3]. Non-medical higher education institutions (in particular, Ukrainian Engineering Pedagogics

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Academy (UEPA), National Technical University "Kharkiv Polytechnic Institute" (NTU "KhPI"), V.N. Karazin Kharkiv National University, Ukraine), invite such specialists for systematic teaching at departments of the relevant profile or for conducting individual classes [4; 5]. In Kharkiv, the disciplines taught in these higher education institutions are "Valeology", "Health Pedagogy" and "Fundamentals of Medical Knowledge and Health-Saving". The latter two disciplines are related as they are built from 14 educational topics that are able to form valeological competence in students within the period of least one academic year. The valeological disciplines "Health Pedagogy" and "Fundamentals of Medical Knowledge and Health-Saving" contain topics, when teachers need to get honest answers about their health status and behavior that may go beyond the law (when using psychoactive substances) and traditional morality (sexual preferences). Answers to these and other questions about the health of students and their family members should be kept confidential, but at the same time not interfere with the assessment of academic performance. The teachers of valeological disciplines should offer students the conditions for confidential collection and use of such information [6; 7].

The **aim** of the study was to develop an algorithm for reliable collection and storage of confidential information regarding the health and behavior of non-medical students.

Materials and Methods

The study was conducted using the sociological method and the method of system analysis. To establish the level of formation of valeological competence, the teacher assessed knowledge, practical skills, motivation for a healthy lifestyle [8], conscious attitude to the norms of a healthy lifestyle and safe behavior, adherence to one's own beliefs about possible diseases of the non-medical students and his family members, hygiene skills, ability to provide emergency pre-hospital care, risk factors for infection, injury, cessation of vital functions, etc. Issues of sexual behavior (preferences, number of sexual partners, use of contraceptives, unwanted pregnancies, sexual violence), sexually transmitted diseases, HIV/AIDS, use of legal and prohibited psychoactive substances, etc. were discussed with the non-medical students in private or through questionnaires. For effective influence (changing behavioral patterns to safer ones, forming a healthy lifestyle), frank answers to questions regarding personal health of students and their family members, the behavioral patterns of students and their sexual partners, are necessary. To obtain frank answers, a teacher with medical practice/medical education (hereinafter referred to as a trusted doctor) had to guarantee the student confidentiality and maintaining of medical secrecy, which is regulated by Article 40 of the Law of Ukraine 2801-XII of 19 Nov 1992 "Fundamentals of Ukrainian Legislation on Health Care" [9]. A test for knowledge of theoretical material of the valeological discipline and practical skills in solving situational tasks during the study of most topics of the valeological disciplines "Health Pedagogy" and "Fundamentals of Medical Knowledge and Health-Saving" was combined with a questionnaire. The use of this confidential technique was tested on more than 4,000 non-medical students between 2004 and 2024.

Results and Discussion

In March 2020, due to the COVID-19 pandemic, many higher education institutions in Ukraine were forced to switch to distance or blended learning [10]. In February 2022, the need to comply with quarantine measures was added to the risk of death of higher education students and teachers during the educational process from shelling by the russian terrorist army that attacked Ukraine. These facts increase the prospect of continuing distance learning in the coming years and push for the creation of new methods of ensuring confidentiality. Distance learning provides sufficient technical capabilities to meet these conditions, and even simplifies private communication between a non-medical student and a teacher.

Confidentiality issues are the most well-established in medical practice. During communication between a doctor and a patient, the doctor immediately offers a model that allows the patient to feel safe to answer the doctor's questions frankly [11]. During communication between a teacher and a non-medical student, similar conditions are created specifically within the framework of individual pedagogical research. And confidentiality conditions do not apply to pedagogical practice by default. The greatest demand for the creation of confidentiality conditions exists precisely in disciplines that provide for psychological and medical examination of non-medical students [12; 13].

The ethics of biomedical research with humans require anonymous surveys where possible. However, anonymous surveys do not correspond to the methodology for forming valeological competence by the disciplines "Health Pedagogy" and "Fundamentals of Medical Knowledge and Health-Saving " for the following reasons:

1) to form valeological competence, it is necessary to master the entire program of the discipline, which consists of 14 topics;

2) on 8 out of 14 topics, non-medical students must be asked personal questions, the answers to which must be kept confidential;

3) to assess the success of the formation of valeological competence of each non-medical student, the teacher must evaluate the answers to all questionnaires developed for each of the topic of the discipline, which is impossible to do in the case of an anonymous survey.

Confidential information received by the trusted physician was stored in a way that prevented access to it by unauthorized persons. Maintaining confidentiality when using both paper and electronic questionnaires was achieved through the following steps:

1) all pages of paper questionnaires-tests that required students' answers were filled out simultaneously (their questions are logically interconnected within each topic studied in the course of the disciplines "Health Pedagogy" and "Fundamentals of Medical Knowledge and Health-Saving"), but were stored separately;

2) the test-questionnaire contains separate blocks of information in the following sequence:

- demographic part, which indicates the date of filling out the questionnaire (first, second, or third time it is filled in), surname, first name and patronymic of the non-medical student, date of birth in the form dd.mm.yyyy, age (in full years), sex, course, group, e-mail address;

- the test part of the test-questionnaire, which contains the answers of student to theoretical questions and solutions to situational tasks, and is subject to academic evaluation;

- the questionnaire part of the test-questionnaire, which may contain confidential questions and is not subject to academic assessment, except for the self-examination skills of the student; the questionnaire part begins with an arbitrary code consisting of a randomly generated sequence of letters and numbers that are not related to the academic group, or the age of student, any other personal data of the student, by which this student can be uniquely identified among all other students; the questionnaire part begins with a new sheet so that it can be mechanically separated from the test part and the code key of the test-questionnaire; the questions of the questionnaire part are answered by the student, the code is invented and entered into the questionnaire part by a trusted doctor, until the test part of the questionnaire is separated from the questionnaire part and from the code key; the questionnaire part of the test-questionnaire without personal data of the student is anonymous, which meets bioethical requirements for medical research involving humans [14, p. 50];

- code key – the part of the test questionnaire, which is stored by a trusted doctor in a personal safe, and contains the passport data of the student and an arbitrary code assigned to the questionnaire part of the test-questionnaire; the code key of the test-questionnaire is filled in personally by the trusted doctor; the code key of the test questionnaire begins with a new sheet so that it can be mechanically separated from the test and questionnaire parts of the test-questionnaire.

The student's answers to the test-questionnaire allow the trusted doctor to provide recommendations on reducing the risks of diseases and injuries, if necessary, refer the student for consultation with a doctor of the appropriate profile or for examination in a laboratory [15–17]. This mechanism reflects the connection between the system of valeological education and the public health system of the country [18]. The questionnaire part of the text-questionnaire contains the data on the state of health, life history, family history, stigmatizing diseases and the results of their treatment, the psychological and mental state of the applicant for non-medical student, sexual behavior, cases of violence, and the use of prohibited psychoactive substances. Access to all questionnaires allows the teacher to comprehensively assess the behavior of the applicant for student. At the same time, only the test parts of the test-questionnaires were freely available to the department management, other teachers, technical staff, and the administration of the university (hereinafter referred to as third parties). The data from the questionnaire parts of the tests were summarized (statistically processed) in a form that excluded the identification of the student by characteristics that obviously distinguished him from other students. This approach required a certain autonomy of the teacher of the valeological discipline and trust in his decisions by the university administration [19].

Work with test-questionnaires could be carried out both on paper and in electronic form. Paper test-questionnaires were later converted to electronic form. After that, paper media were destroyed. Converting the questionnaire from paper to electronic form reduced the risks of third parties becoming familiar with the confidential results of the questionnaire, reduced the costs of storing the questionnaires (safes, special archives using large

areas, and the work of an archivist were not required). Also, such storage excluded the possibility of identifying the applicants who filled out the questionnaire part of the test-questionnaire by handwriting.

The most popular system for planning and evaluating the results of the educational process is Moodle [20–22], which also allows you to create questionnaires. But questionnaires in Moodle are stored in an unencrypted form, and the results of the questionnaire are available to many participants in the educational process (the student himself, the teacher, the head of the department, the management of the higher education institution, in some cases – also to specialists of the Ministry of Education and Science of Ukraine and the National (of Ukraine) Agency for Higher Education Quality Assurance, who carry out the inspection of educational institutions, if they have access and have created appropriate accounts on the university's distance education website. Learning using distance education websites also involves the use of other Internet platforms and services, which can be both integrated and non-integrated with Moodle. In the latter case, the assessment and text conclusion regarding the academic result of the test (knowledge, ability to solve situational tasks) cannot contain data that is reported to the trusted doctor in the confidential part of the test-questionnaire. The assessment and text conclusion regarding the questionnaire, which reflects the academic result of the questionnaire, but does not concern its confidential content, can be entered into Moodle by the teacher manually (not automatically).

For surveys on other platforms, Google Forms is most often used. Flexible settings for summarized survey results using Google Forms scripts [23–25] allow you to process survey results in a confidential manner for the purposes of personal counseling, and anonymously for statistical processing of a set of questionnaires for scientific purposes.

In order to comply with the principles of anonymity and confidentiality, it is necessary to determine how Ukrainian legislation defines the content of these concepts. Due to the frequent discrimination and stigmatization of HIV-infected/AIDS patients, the details of anonymity and confidentiality of counseling in Ukrainian legislation are best worked out for this category of patients. The Law of Ukraine "On Combating the Spread of Diseases Caused by the Human Immunodeficiency Virus (HIV), and Legal and Social Protection of People Living with HIV" [26] grants patients the right to anonymous counseling on HIV infection (Article 4, Clause 1, Clause 4). Confidentiality is understood as the preservation by the counselor of information received from the patient: the fact of the person's application, the content of the services received, the result of the examination, data on the patient's personal life, and his passport data. Confidential information may be transferred to third parties in cases clearly defined by law: in relation to a minor or incapacitated patient – to parents or legal guardians, for the purpose of further examination and treatment – to health care institutions, for the purpose of revealing or preventing a criminal offense – to the prosecutor's office, investigation, inquiry and court bodies (upon a reasoned written request). Disclosure of confidential information by a medical or auxiliary worker, official who received such information in connection with the performance of their official duties or arbitrarily, entails criminal liability. When preparing, using and storing documentation containing confidential information about HIV-infected persons, medical workers, administrative and auxiliary personnel of medical institutions must prepare reports and speak in the media in such a way that HIV-infected persons are not identified. Such identification and disclosure of confidential information can lead to alienation and discrimination of the HIV-infected person by the family and society. The use of confidential documentation is carried out in such a way as to prevent unauthorized persons from getting acquainted with it, using archives, safes and drawing up appropriate orders from the head on the appointment of consultants. If the medical record (medical history) is stored in the file cabinet (archive) of a medical institution that does not belong to the Ukrainian network of AIDS prevention and control centers (these institutions maintain dispensary records only of HIV-infected people and children born to HIV-infected mothers), the codes assigned to HIV-infected people of various categories in accordance with the Order of the Ministry of Health of Ukraine No.120 [27] (HIV-infected pregnant women – code 109, HIV-infected injection drug users – code 102, etc.) are prohibited from being placed on the cover of the medical record (medical history) so that they cannot be seen by unauthorized persons.

The current Procedure (Protocol) for voluntary counseling and testing for HIV infection [28] provides for the possibility of receiving anonymous counseling by the patient, which takes place wi-

thout determining the patient's passport data (surname, first name, patronymic; date of birth; place of residence, work or study, etc.). In the questionnaire, this data is replaced by a code necessary to obtain the results of the examination. Counseling should also be accessible. Discussion of the HIV status of students who have contacted a teacher with medical education/medical practice who teaches the valeological discipline should also take place in compliance with the principles of anonymity and confidentiality, and the opportunity to discuss HIV status will contribute to timely referral to specialized medical institutions for HIV testing and correction of behavioral patterns to reduce the risk of infection. Counseling may be extended to spouses, fiancés, sexual partners, family members, friends, colleagues, etc. only with the patient's consent (clause 5, article 4 of the Order of the Ministry of Health No.415). It is desirable that the pre-test and post-test counseling of the patient be conducted by the same counselor. The result of counseling in the presence of a positive HIV test should be an invitation to examine the sexual partner of the HIV-infected person, if the HIV-infected person agrees to inform him of the test result. If the HIV test was not anonymous, the HIV-infected person must sign a document certifying his awareness of the criminal liability for endangering infection and infection of other persons with the human immunodeficiency virus.

A similar understanding of confidentiality and anonymity exists in other areas of medical practice: during the termination of unwanted pregnancy [29], in other matters of family planning (in particular, contraception) [30], including in "youth-friendly clinics" [31], in the presence of stigmatizing sexually transmitted diseases and the vulnerable position of prisoners [32], in the laws of Ukraine "On Information" (Article 11, paragraph 2) [33], "Fundamentals of Ukrainian Legislation on Health Care" [34] (Article 40), "On Personal Data Protection" [35] (Article 6, paragraph 8; Article 7, paragraph 1; Article 7, paragraph 2, paragraph 6). From a technical point of view [36], confidentiality is the property of information to be received only by an authorized user or process.

Access to confidential information in computer networks is administered on the basis of trust. The principle of delimiting access to information is natural for computer systems, so its use by means of computer communication during forced distance learning simplifies the task of ensuring confidentiality. This fact prompted our research group to necessarily translate paper tests of the questionnaire into electronic form. And the imperfection of the Moodle platform in terms of confidentiality has confused teachers with medical education to look for ready-made solutions on other platforms. Convenient ready-made solutions turned out to be Google Forms and Google Apps Script [37]. They are used in parallel with Moodle in accordance with the academic rules of UEPA and other universities, which taught the valeological disciplines "Health Pedagogy" and "Fundamentals of Medical Knowledge and Health-Saving".

Work with paper and electronic questionnaires has thus been synchronized and now consists of four stages:

1) collecting information (surveying and testing);

2) division of information into confidential and non-confidential;

3) storage and evaluation of information;

4) constant access to information.

Working with information obtained from non-medical students of UEPA in the form of questionnaire tests during the study of the valeological discipline "Health Pedagogy" showed that the proposed method of maintaining the confidentiality of information led to an increase in the trust of students in the teacher of the discipline "Health Pedagogy", as evidenced by a decrease in the number of rejected questionnaires due to unreliable answers in the 2021/2022 academic year compared to the 2020/2021 academic year by 2.5 times – from 11.8% to 4.7%. To check the reliability of the questionnaires, special "trap" questions were included in them: essentially the same, but different in the wording of the questions. The questionnaire was considered reliable only if the answers to such questions coincided. We also rejected the questionnaires of students who did not fully study the course of the discipline, who did not study consistently throughout the semester, but quickly completed all the tasks of the discipline on the last day before the exam, and who were suspected of academic dishonesty (copying other people's works).

The proposed algorithm satisfied all the requirements for conducting confidential research and allows its use in further valeological research during the training of non-medical students.

Conclusions

1. Confidentiality of information about the health and diseases of non-medical students, obtained by a teacher of valeological disciplines of engineering universities of Ukraine for academic purposes, is a prerequisite for honest answers to personal questions, without which it is impossible

to fully assess the success of the formation of valeological competence, and therefore to fairly assess the academic success of non-medical students.

2. We propose combining the pedagogical process with medical consultation by a teacher with medical education/medical practice (trusted doctor); combining academic test questions on knowledge and practical skills of health preservation and health restoration with a questionnaire on risk factors for diseases, family history, life history, behavioral patterns, healthy lifestyle, treatment results, – with further separation of these data for assessing academic results, studying personal health issues and generalization with statistical processing for scientific purposes; encryption of personal data with Google Forms scripts to enable confidential consultations instead of anonymous ones. To maintain confidentiality, encryption of personal data and restriction of access to personal information are used.

3. For confidential storage of questionnaire data, encryption of the student's personal data and separation of access to confidential and non-confidential data using standard Google scripts were used. Forms, which allows you to use confidential questionnaires instead of anonymous ones. For scientific purposes, the questionnaire data is statistically processed as anonymous. If necessary, use standard scripts of the Google Forms allows you to decode the data of the code key of different questionnaires of one applicant for higher non-medical education, identify him to obtain a comprehensive picture of his current state of health and the level of formation of valeological competence. The proposed methodology reduced the number of rejected questionnaires due to unreliable answers in the 2021/2022 academic year compared to the 2020/2021 academic year by 2.5 times.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations rele-vant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

Funding Sources

There are no external sources of funding.

Consent for publication

All authors give their consent to publication.

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Received: 04 Oct 2024
Accepted: 31 Dec 2024

Cite in Vancouver style as: Shevchenko AS, Shtefan LV, Lytvynenko MV, Yushko TG, Brown GW, Tishchenko OM. Ethics of valeological research in higher education institutions. Inter Collegas. 2024;11(4):49-56. https://doi.org/10.35339/ic.11.4.ssl

Archived: https://doi.org/10.5281/zenodo.14755070

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