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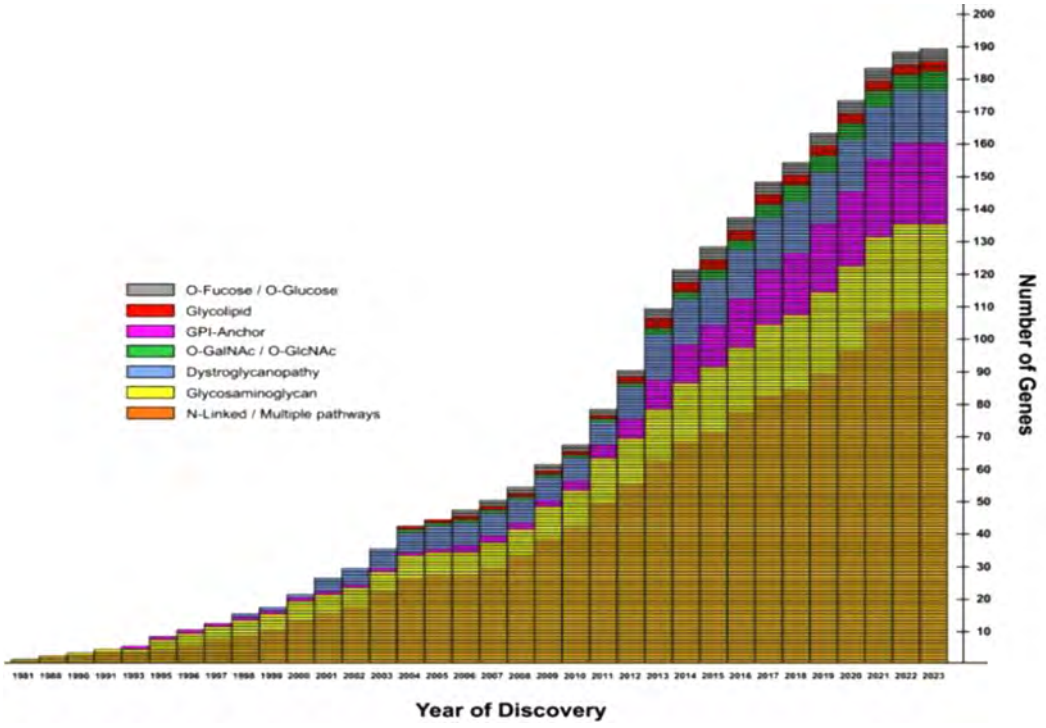
CONTENT HIGHLIGHTS:

Daniela Blăniță, Chiril Boiciuc, Alina Nicolescu, Victoria Sacara, Natalia Ușurelu
Congenital disorders of glycosylation – diagnosis experience in the Republic of Moldova



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RESEARCH ARTICLE

Congenital disorders of glycosylation – diagnosis experience in the Republic of Moldova

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ABSTRACT

Introduction. Congenital disorders of glycosylation (CDG) represent a group of rare diseases with multisystem involvement and exponential expansion, characterized by defects in the glycosylation process, which is essential for the proper functioning of proteins and lipids. These often manifest under the guise of other pathologies. The objective of the study was to diagnose CDG using Isoelectric Focusing of Transferrin (IEFT) in the Republic of Moldova and to identify diseases that mimic CDG.

Material and methods. Following medical-genetic consultations at the Institute of Mother and Child, 320 patients suspected for CDG were selected. History, clinical and paraclinical data were collected, and the proposed research questionnaire was completed. After signing the informed consent, the biological samples (serum, plasma, urine, DNA, DBS) were collected from all patients. Screening serum using the IEFT method was performed for 150 patients due to limited availability of reagents. For cases with negative CDG results, selective molecular-genetic tests such as MLPA, CGH-array, WES/WGS were performed.

Results. Clinical and paraclinical examination of patients suspected CDG revealed multisystem involvement in 99.1% of cases, predominantly affecting the central nervous system in 92.2%. System and organ evaluation showed that, in addition to neurological damage there were skeletal (22.5%), renal (10.9%), ophthalmological (38.8%), muscular (22.5%), hepatic (20.9%), cardiac (40.6%), auditory (5.9%), pulmonary (3.8%), and gastrointestinal (29.4%) involvement. Analysis of 150 serum samples by IEFT method identified 3 positive cases for CDG. Molecular genetic testing revealed additional two CDG cases with negative IEFT and over 50 rare pathologies that manifest under the guise of CDG.

Conclusions. Clinical heterogeneity and disruptions in various biological pathways contribute to the complexity of CDG diagnosis. The clinical overlap of genetic diseases represents a considerable challenge for clinicians, as similar symptoms between different genetic conditions can lead to confusion and delay in identifying the disease.

Keywords: CDG, IEFT, multisystem involvement, WES/WGS.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

The genetic basis of Congenital Disorders of Glycosylation (CDG) remains incompletely understood, requiring further research to clarify molecular mechanisms, regional genetic variations, and genotype-phenotype correlations. Additionally, exploring the therapeutic implications of genetic profiles and long-term prognosis, especially in complex cases, is essential for improving diagnosis and treatment.

The research hypothesis

This research explores the effectiveness of the Isoelectric Focusing of Transferrin method in diagnosing CDG, analyzes the clinical spectrum of patients suspected of CDG and highlights the challenges of diagnosing these conditions in the Republic of Moldova.

The novelty added by manuscript to the already published scientific literature

Our study highlights the clinical diversity of patients suspected of CDG in the Republic of Moldova, demonstrating the complexity of diagnosing these conditions. The research emphasizes the utility of applying Isoelectric Focusing of Transferrin as a screening method and other advanced genetic testing in correctly identifying detected CDG cases.

Introduction

Congenital disorders of glycosylation (CDG) are a group of rare metabolic disorders, with multisystem impairment that result from disturbed protein and lipid glycosylation. The first case was clinically reported in 1980 by Jaeken *et al.* [1]. With the advent of next-generation sequencing methods in the early 2010s, the identification of CDG types has increased exponentially Currently, there are approximately 200 types of CDG with 189 phenotypes (fig.1) [2, 3]. The prevalence of this group of pathologies is estimated to be less than 1 per 100.000 in Europe [4].

Based on the mode of action, the CDG is classified in 8 categories:

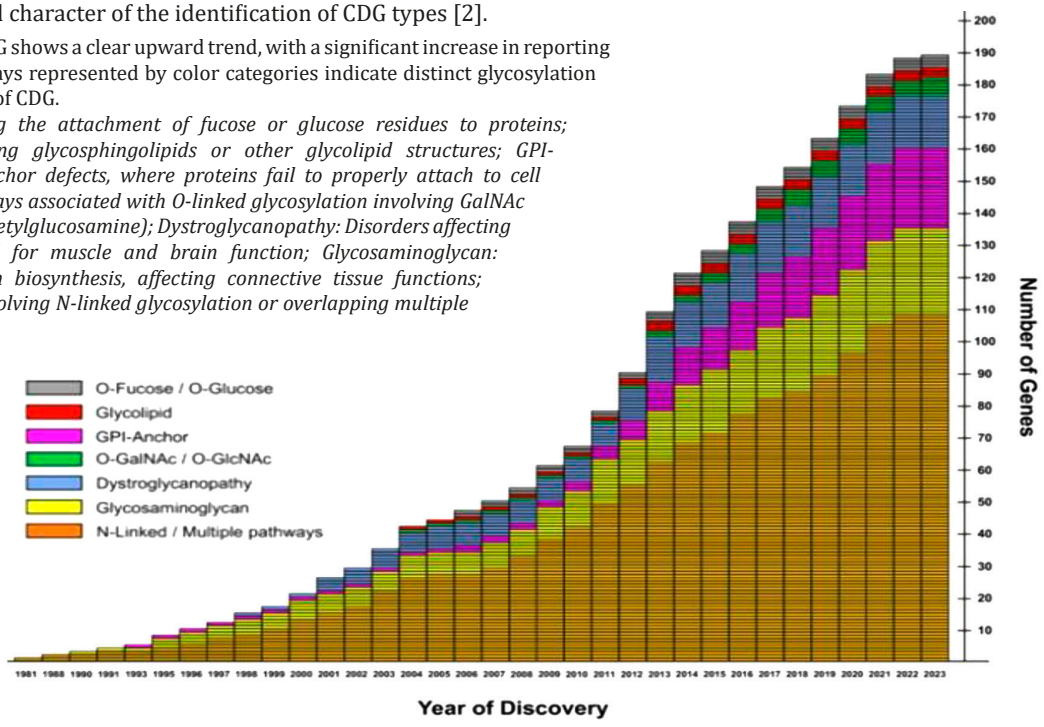
1. Disorders of monosaccharide synthesis and interconversion;
2. Disorders of nucleotide sugar synthesis and transport;
3. Disorders of N-linked protein glycosylation;
4. Disorders of O-linked protein glycosylation;
5. Disorders of lipid glycosylation;
6. Disorders of vesicular trafficking;
7. Disorders of multiple glycosylation pathways;
8. Disorders of glycoprotein/glycan degradation [2].

Considering that CDG is a group of pathologies with multisystem damage, 19 involved organ systems has been described by BG Ng *et al*. The most affected was the nervous system in 81%, followed by ocular in 46% and muscular in 53%. The dysmorphic features were revealed in 56% [2]. Since 1984, Isoelectric focusing of transferrin (IEFT) has been considered a biochemical method used to detect abnormalities in transferrin glycosylation, making it a key screening tool for diagnosing Congenital Disorders of Glycosylation (CDG), particularly those involving N-glycosylation [1, 5]. IEFT is a specialized electrophoretic technique that separates transferrin isoforms based on their isoelectric point, which depends on the number of sialic acid residues attached to its N-glycans. Following the analysis of IEFT results, two pathological transferrin profiles can be identified: type I and type II. The IEFT type I profile is associated with defects in the endoplasmic reticulum, while the type II profile is linked to abnormalities in the Golgi apparatus.

Fig. 1 The exponential character of the identification of CDG types [2].

The number of genes associated with CDG shows a clear upward trend, with a significant increase in reporting starting from 1981 to 2023. The pathways represented by color categories indicate distinct glycosylation types, reflecting the genetic complexity of CDG.

O-Fucose/O-Glucose: Pathways involving the attachment of fucose or glucose residues to proteins; Glycolipid: Refers to disorders involving glycosphingolipids or other glycolipid structures; GPI-Anchor: Glycosylphosphatidylinositol anchor defects, where proteins fail to properly attach to cell membranes; O-GalNAc/O-GlcNAc: Pathways associated with O-linked glycosylation involving GalNAc (N-acetylgalactosamine) or GlcNAc (N-acetylglucosamine); Dystroglycanopathy: Disorders affecting glycosylation of dystroglycan, essential for muscle and brain function; Glycosaminoglycan: Pathways related to glycosaminoglycan biosynthesis, affecting connective tissue functions; N-Linked/Multiple Pathways: Defects involving N-linked glycosylation or overlapping multiple glycosylation pathways.



However, normal results do not exclude CDG, as some types may present with mild or absent transferrin abnormalities. This is why IEFT remains an essential first-line biochemical screening tool for CDG but should always be followed by molecular diagnostics for a definitive diagnosis [6].

The objective of this study is to diagnose CDG using Isoelectric Focusing of Transferrin in the Republic of Moldova and to identify diseases that mimic CDG.

Material and methods

The selective cross-sectional observational descriptive study was conducted at the Institute of Mother and Child, in the Laboratory of Prevention of Hereditary Pathologies from October 2018 to April 2024. The inclusion criteria for the study encompassed children with multisystem involvement of unclear etiology, defined by the following characteristics: age between 3 months and 18 years, psychomotor and growth retardation, muscle hypotonia, seizures, dysmorphic features and with chromosomal abnormalities excluded. These manifestations were accompanied by the involvement of other organs and systems, including but not limited to the cardiovascular, hepatic, musculoskeletal, ophthalmologic, dermatologic, immune, and endocrine systems. The exclusion criteria included children with multisystem involvement of confirmed etiology, viral hepatitis, and transferrin polymorphism in IEFT. Following the medical-genetic consultations at the Institute of Mother and Child in the Republic of Moldova and a comprehensive evaluation, including medical history, psychomotor development assessment, physical examination, 320 patients were selected according to the inclusion criteria and enrolled in the study. All patients have signed the consent for participation (approved by Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy Minutes No. 45, from July 03, 2019. For each included patient there was completed a questionnaire noting the clinical, phenotypical and investigational features. The biological samples were collected, including serum, plasma, urine, DNA, and DBS. The screening of 150 patients was performed using the IEFT method. For differential diagnosis of other diseases mimicking CDG, metabolic work-up (amino acids in blood, organic acid in urine, acylcarnitine profile) and selective MLPA, CGH-array, and SNP/WES/WGS have been performed. The diagnostic algorithm for CDG and mimicking pathologies was developed in accordance with the innovation act "Algorithm for the evaluation of children with multisystem involvement for the diagnosis of Congenital Disorders of Glycosylation" No. 555 from 29.07.2024. The database has been created using Microsoft Office Excel (Microsoft Corporation, Excel, version 2010, WA, USA), and IBM SPSS Statistics 28.0 program was used for the descriptive statistics to investigate the characteristics of the entire cohort.

Results

A total of 320 individuals were enrolled in the study. Due to the multisystem involvement, the clinical presentation of the patients included in the research exhibited significant variability. One hundred forty-two individuals (44.4%) were female, and 178 (55.6%) were male. The range of age was around 3-216 months, the mean age was 44 months. The clinical heterogeneity revealed the involvement of 13 affected systems, the leading system being attributed to central nervous system. The second place is hematological system followed by cardiovascular, ophthalmological, gastrointestinal, muscular, skeletal, hepatic, endocrine, renal, urological, auditory, pulmonary and immunological (tab. 1, fig. 2).

The predominant complaints reported by study group showed the following incidences: fatigue in 280 patients (87.5%) (95% CI 0.84-0.91), low attention 250 (78.1%) (95% CI 0.74-0.83), concentration disorders 246 (76.9%) (95% CI 0.73-0.82), verbal retardation 223 (69.7%) (95% CI 0.65 - 0.75), failure to thrive 151 (47.2%) (95% CI 0.43-0.54), dehydration 65 (20.3%) (95% CI 0.17-0.26) and others. Regarding the inclusion criteria in the study, seizures have been registered in 161 patients (50.3%) (95% CI 0.45-0.56), psychomotor retardation – in 275 (85.9%) (95% CI

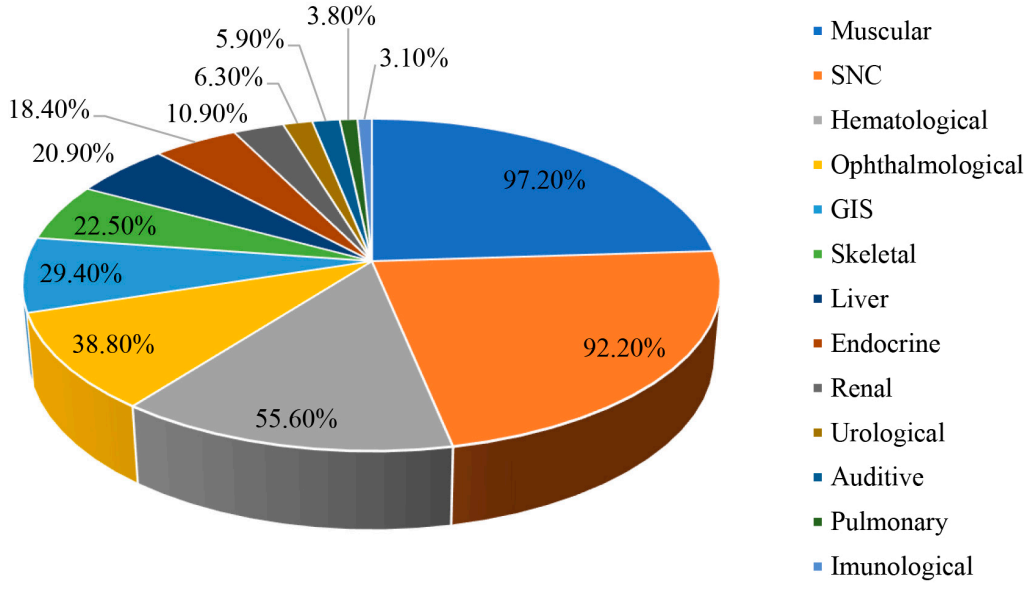


Fig. 2. The multisystem affection in investigated Moldovan cohort suspected for CDG

The pie chart illustrates the distribution of multisystem involvement among studied patients. Each segment represents a specific organ or system affected, along with the corresponding percentage of patients exhibiting symptoms in that system.

0.83-0.91), failure to thrive – in 199 (62.2%) (95% CI 0.58-0.68), muscle tone disorders – in 310 (96.9%) (95% CI 0.95-0.99), dysmorphic features – in 197 (9.7%) (95% CI 0.57-0.67), and totally of them 317 (99.1%) (95% CI 0.98-1.00) had multisystem involvement.

After a comprehensive clinical examination, the suspected CDG cases were screened by IEFT. In three cases of 150 patients, positive IEFT has been found. Metabolic work-up and molecular genetic studies were undertaken to finalize the diagnosis. After metabolic work-up, in one case, significant galactose levels in plasma were found, as well as galactitol in urine, suggestive for Galactose troubles. Another two cases revealed no particular metabolites. Then, molecular genetic testing by Sanger sequencing using the Genetic Analyzer 3500, manufacturer Applied Biosystems was undertaken, which revealed mutations in the *ALDO B* gene in two positive IEFT cases and the *GALT* gene in the other positive case, validating the diagnosis of Hereditary Fructose Intolerance and Galactosemia, respectively. In other two patients with IEFT negative, a mutation in the *GNE* gene was discovered by WGS, confirming GNE myopathy (tab.2) [7].

Table 1. Clinical variability in patients enrolled in study.

Affected systems	№ patients	Frequency (%)	95% confidence interval
Neurological	295	92.2	0.18-0.27
Hematological	178	55.6	0.51-0.62
Cardiovascular	130	40.6	0.35-0.46
Ocular	124	38.8	0.34-0.44
Gastrointestinal	94	29.4	0.24-0.34
Muscular	72	22.5	0.18-0.27
Skeletal	72	22.5	0.18-0.28
Hepatic	67	20.9	0.17-0.26
Endocrine	59	18.4	0.14-0.23
Renal	35	10.9	0.07-0.14
Genitourinary	20	6.3	0.04-0.09
Audiological	19	5.9	0.03-0.09
Respiratory	12	3.8	0.02-0.06
Immunological	10	3.1	0.01-0.05

Note: *CDG – Congenital disorders of Glycosylations; Nr – number of affections patients; 13 affected systems, the central nervous system being most frequently affected. The least affected systems are urological, audiological, respiratory and immunological. However, their presence still highlights the variability of CDG presentations and the need for a multidisciplinary diagnostic approach. Overall, the table underscores the complexity of CDG, emphasizing the importance of comprehensive clinical evaluations for accurate diagnosis and management.*

For 50 cases with negative IEFT, complementary tests such as MLPA (5 cases) and WGS (49 cases) allowed for exclusion of CDG and the confirmatory diagnosis of other diseases. For the remaining cases, it was not possible to obtain additional diagnostic information due to limitations in access to confirmatory testing in our country.

Discussions

CDG constitute a group of multisystem hereditary pathological conditions characterized by dysfunctions in the glycosylation process in the Endoplasmic Reticulum (ER) and the cellular Golgi Apparatus (AG). These dysfunctions affect the biosynthesis of glycoproteins and other glycoconjugates, significantly influencing their functionality. The scientific progress in genetics have facilitated the widespread use of high throughput sequencing methods, allowing scientists to identify the molecular etiologies of CDG and increasing the frequency of diagnosis since the first identifications in the 1980s [8]. Despite advances in the field, the incidence and prevalence of all types of CDG have not yet been precisely established.

Table 2. Types of CDG diagnosed in Republic of Moldova.

Patients	IEFT results	Gene	Mutations	Disease (ORPHA code)
P1	Positive	*ALDO B*	[c.[113-1-115d/l]/ [c.[113-1-115d/l]	Hereditary fructose intolerance (ORPHA:469)
P2	Positive	*GALT*	P.E203L/E203L	Galactosemia (ORPHA:352)
P3	Positive	*ALDO B*	c.[113-1-115d/l]/ [524C>A]	Hereditary fructose intolerance (ORPHA:469)
P4	Negative	*GNE*	c.*1014_*1037du pCACACACACACA CACACACACACA*/ c.1767A>Gp.(=)	GNE myopathy (ORPHA:602)
P5	Negative	*GNE*	c.173 C>T/c.196G>A	GNE myopathy (ORPHA:602)

Note: *CDG – Congenital disorders of Glycosylations; IEFT – Isoelectric Focusing of transferrin; ORPHA - reference portal for information on rare diseases and orphan drugs; P - number of patients, ALDOB - Aldolase B, Fructose-Bisphosphate, GALT - Galactose-1-Phosphate Uridylyltransferase, GNE - Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase. The total 5 cases of CDG were diagnosed. Three cases were IEFT positive, and two cases IEFT negative. The mutation in ALDO B, GALT and GNEs gene were determined.*

Research in this field has led to conflicting opinions among scientific groups. Until recently, Hereditary Fructose Intolerance and Galactosemia were considered secondary abnormalities of the glycosylation process, being excluded from the list of CDG [9, 10]. However, in May 2024, these conditions were reclassified as CDG spectrum disorders, being attributed to derangements in monosaccharide synthesis and interconversion [2].

In the reported types of CDG, the most prevalent symptoms were neurological (80,5%), followed by dysmorphisms (55.6%), endocrine symptoms (55%), skeletal abnormalities (52.7%), ocular problems (46.3%), digestive issue (34.1%), cardiovascular abnormalities (22.0%), muscular problems (11.7%), respiratory issues (10.2%), genitourinary problems (9.8%), psychiatric symptoms (9.8%), renal complications (8.3%), hair-related issues (6.8%) and dental problems (4.4%) [2, 11].

In Moldovan cohort of CDG suspected patients, the most commonly affected systems were neurological and hematological, followed by cardiovascular, ophthalmological, gastrointestinal, skeletal, hepatic, endocrine, renal, urological, auditory, pulmonary, and immunological. The dental, hair-related, psychiatric, and dermatological symptoms were not reported in our cohort.

Considering that CDG is a group of ultra-rare pathologies with multisystem disorder, often mimicking other genetic diseases, they are frequently underdiagnosed. In the diagnostic process, it is necessary to follow a staged diagnostic algorithm that requires a differential diagnosis to be carried out as meticulously as possible. The most important groups of pathologies that must be excluded are Mitochondrial Diseases and Disorders of Phospholipid Synthesis, both of which also involve multisystem damage [12]. At the same time, dysmorphic features related to a frequency of 55.6% in CDG, can often be found in other pathologies. The presence of fat pads can most commonly be seen in PMM2-CDG, and it has also been reported in Wiedemann-Rautenstrauch syndrome (neonatal progeria). Also, the presence of inverted nipples can occasionally be determined in other genetic diseases than CDG, such as Turner, Smith-Lemli-Opitz, Weaver and Robinow syndrome. Almond-shaped eyes can often be found in Prader-Willi syndrome, which is accompanied by hypotonia and feeding problems in childhood, which can also be seen in CDG [12]. Among the forms of CDG that involve liver damage, the differential diagnosis algorithm includes other various genetic diseases and inborn errors of metabolism as Alpers progressive infantile poliodystrophy, alpha-1 antitrypsin deficiency, cystic fibrosis, Gaucher disease, type IV glycogen storage disorder, glycerol dehydrogenase-1-deficiency-3-phosphate, hemochromatosis, 3-hydroxyacyl-CoA dehydrogenase deficiency, lysosomal acid lipase deficiency, Niemann-Pick disease type A, B, C, peroxisomal diseases, S-adenosine homocysteine hydroxylase deficiency, tyrosinemia type I, and Wilson's disease [13]. Protein-lipid enteropathy, described especially in MPI-CDG, can also be found in severe celiac disease, congenital intestinal diseases and in various genetic diseases (Noon disease, Turner disease, skeletal dysplasia FGFR3). When an endocrine disorder is observed with predominance of hypoglycemia, it is necessary to carry out the differential diagnosis between fatty acid beta-oxidation defects, glycogen storage disorders, the average form of Beckwith-Wiedemann syndrome, congenital hypopituitarism and congenital adrenal hyperplasia [13]. In the presence of renal damage, it is recommended to exclude tubulopathies of metabolic cause, diseases with energy deficit and metabolic disorders of the storage type of complex molecules, as well as other genetic syndromes accompanied by polycystic kidney disease and nephrotic syndrome [12].

One of the objectives of our study was to identify pathologies that mimic the clinical manifestations of CDG. In the analyzed cohort, mitochondrial diseases were diagnosed in 6 cases, representing a significant percentage of the pathologies confused with CDG because of their multisystem affection. Prader-Willi syndrome was identified in 2 cases, and Angelman syndrome, Zellweger syndrome, and Wilson disease were each diagnosed in one case. Other neurological diseases that mimic CDG were determined by next generation sequencing (tab. 3). These genetic pathologies although have clinical manifestations similar to CDG, show distinct pathogenetic mechanisms, emphasizing the importance of a rigorous and differential diagnostic evaluation in the management of these complex conditions.

Table 3. The diseases determined in our cohort that mimic CDG.

Gene	Diseases that mimic CDG	OMIM/ORPHA CODE	Cases
PPP2R5D	Jordan Syndrome	OMIM 616355/OPRHA 457279	1
ALDH7A1	Pyridoxine-dependent epilepsy	OMIM 1617290 /OPRHA3006	1
TSEN54	Pontocerebellar hyperplasia type 2A	OMIM 277470/OPRHA 2524	2
SOX11	Coffin-Sirris Syndrome	OMIM 615866/ORPHA 1465	1
AR	Kenedy spinal and bulbar muscular atrophy	OMIM 313200/ORPHA 481	1
FOXG1	Congenital Rett Syndrome	OMIM 613454/ORPHA	1
PEX1	Zelweger Syndrome	OMIM 214100/ORPHA 912	1
WHSC1	Wolf-Hirschhorn Syndrome	OMIM 194190/ORPHA 280	1
ELN	Wiliams Syndrome	OMIM 194050/ORPHA 904	1
LAMA2	Congenital muscle wasting with myosin deficiency	OMIM 607855/1ORPHA 258	1
OPA1	Mitochondrial DNA depletion syndrome	OMIM 616896/ORPHA 369897	1
MTATP6	Sindromul Leigh	OMIM 256000/2ORPHA 506	2
SCN2A	Epileptic and developmental encephalopathy type 11	OMIM 613721/ORPHA	2
ANO5	Autosomal recessive muscular dystrophy of the limbs	OMIM 611307	1
SMARCAL1	Schimke Syndrome	OMIM 242900/ORPHA 1830	1
Deletion of the 15q11 region	Angelman Syndrome	OMIM 105830/ ORPHA 72	1
Deletion 15q11-q13	Prader-Willi syndrome	OMIM 176270/ORPHA 739	2
GBA	Gaucher disease type 2	OMIM 230900 /ORPHA 77260	1
SMN1	Spinal muscular atrophy	OMIM 253300/ORPHA 253300	2
RALA	Hiatt-Neu-Cooper syndrome	OMIM 619311/ORPHA 528084	1
PAH	Phenylketonuria	OMIM 261600/ORPHA 79254	3
ATP7B	Wilson disease	OMIM 277900/ORPHA 509	1
SCN8A	Cognitive impairment with or without cerebellar ataxia	OMIM 614306	2
HFE	Hemochromatosis	OMIM 465508/ORPHA235200	1
TWNK	Progressive external ophthalmoplegia with mitochondrial DNA deletions	OMIM 609286/ORPHA254892	1

SCNA1	Epileptic encephalopathy, type 6	OMIM619317/ORPHA36387	
NSD1	SOTOS syndrome	OMIM617169/ORPHA 821	1
TGFBR1	LOEYS-DIETZ syndrome	OMIM613795 /ORPHA60030	1
mtTL1	MELAS disease	OMIM 540000 /ORPHA 550	1
SLC9A3R1	Nephrolithiasis/Hypophosphatemic osteoporosis type 2	OMIM612286/ORPHA 244305	1

Note: *OMIM - Online Mendelian Inheritance in Man is a knowledgebase of human genes and genetic disorder; ORPHA - reference portal for information on rare diseases and orphan drugs; CDG – Congenital disorders of glycosylations. The table presents the diagnosed pathologies that mimicked CDG, highlighting the mutations identified in the genes associated with each condition, as well as the number of observed cases.*

According to reported data, IEFT identifies alterations in the transferrin profile in only 60% of cases, primarily in the presence of N-glycosylation defects, however, a normal IEFT result does not rule out CDG [14]. Therefore, in cases with strong clinical and biochemical suspicion, advanced diagnostic approaches such as next-generation sequencing (NGS), including targeted gene panels or whole-exome/genome sequencing (WES/WGS), are recommended as a definitive diagnostic strategy [14, 15]. The remaining 265 cases did not reach a definitive diagnosis due to limited access to diagnostic methods in the Republic of Moldova, as these are very expensive and not performed in our country. In this context, we cannot exclude the possibility that other types of CDG, which test negative on IEFT, may be present in these 265 cases.

Conclusions

Our study revealed significant clinical diversity among patients with suspected CDG, with multisystem involvement and a predominance of central nervous system involvement. Despite the high frequency of symptoms associated with CDG, only three cases were confirmed by IEFT and genetic testing, with final diagnoses of Galactosemia and Hereditary Fructose Intolerance, representing the first group of glycosylation impairment in the novel classification. In addition, two cases were diagnosed with GNE myopathy. Among 50 cases with negative IEFT result, complementary molecular tests allowed the exclusion of CDG and the establishment of other diagnoses. This emphasizes the complexity of diagnosing CDG and the need for a rigorous diagnostic protocol, including advanced metabolic and genetic testing.

Competing interests

None declared.

Authors' contribution

DB conceived conceptualization, methodology, data collection, analysis and interpretation, writing – original draft preparation. CB analyzed the result of screening by IEFT. AN – supervision on differential diagnosis data. VS – coordinator of genetic analysis. NU – research coordinator, conceived writing review and editing, validation. The authors read and approved the final version of the manuscript.

Patient consent

Obtained

Ethics approval

This study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Act No. 45, from July 03, 2019).

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RESEARCH ARTICLE

Thrombosis and hemostatic abnormalities in non-Hodgkin lymphoma

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ABSTRACT

Introduction. Non-Hodgkin lymphoma is a heterogeneous group of malignant lymphoid tumors. Hemostasis disorders in non-Hodgkin lymphoma are often asymptomatic but can develop into severe complications. The risk of venous thromboembolism increases according to the totality of risk factors assessed directly in each individual patient, based on age, gender, comorbidities, performance status, and both congenital and acquired thrombophilia.

Objective. This study aims to evaluate the incidence of hemostasis disorders based on age, gender, NHL type, degree of dissemination, B symptoms, disease onset, tumor size, positivity of anticardiolipin, anti-β2-glycoprotein I, and lupus anticoagulant antibodies, fibrinogen level, lactate dehydrogenase, D-dimers, and Eastern Cooperative Oncology Group performance status.

Material and methods. A total of 161 patients diagnosed with NHL at the Oncology Institute of the Republic of Moldova were evaluated in a prospective cross-sectional descriptive study. Anticardiolipin and anti-β2-glycoprotein I antibodies were measured by enzyme-linked immunosorbent assay, and lupus anticoagulant was assessed by the turbidimetry method. Quantitative testing of D-dimers was performed using automatic latex-agglutination with photometric detection. Plasma fibrinogen levels were assessed by coagulometry. The data were statistically analyzed using Microsoft Excel, GraphPad Prism ver. 9.3.0, Epi Info 7.2, EpiMax Table, and IBM SPSS Statistics version 26.0.

Results. The study included 161 de novo patients, with 48% women and 52% men, and a median age of 59 years. Among them, 56.5% had aggressive non-Hodgkin lymphoma (NHL), and 43.5% had indolent NHL, with a higher prevalence of advanced stages (65.8%). Hemostatic disorders were observed in 10.6% of cases, with venous thromboembolism occurring in 6.7%, more frequently in patients with aggressive non-Hodgkin lymphoma, tumor sizes ≥ 7 cm, a mean age of 50 years, in men (82%), mainly in the first 3-4 weeks, with higher levels of fibrinogen and D-dimer at diagnosis. Anticardiolipin, anti-β2-glycoprotein I, and lupus anticoagulant antibodies were recorded in 3.7% cases of venous thromboembolism cases. Statistical significance was not reached when analyzing thrombosis according to performance status.

Conclusions. The risk of venous thromboembolism in non-Hodgkin lymphoma is dependent on gender, type, tumor size, mediastinal onset, hyperfibrinogenemia, antibody synthesis, and high LDH level. The distribution of patients with non-Hodgkin lymphoma and venous thromboembolism according to disease stage, B symptoms, and performance status was statistically insignificant.

Keywords: lymphoma, hemostatic disorders, thrombosis.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Non-Hodgkin lymphoma is one of the most common malignant lymphoproliferative disorders, with an increasing incidence and prevalence both nationally and internationally. Hemostatic disor-

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ders in non-Hodgkin lymphoma are often asymptomatic but can lead to severe complications. There is limited data available on hemostatic alterations in non-Hodgkin's lymphoma.

The research hypothesis

The risk of associated hemostatic disorders in patients with non-Hodgkin lymphoma is influenced by several clinical and paraclinical factors.

The novelty added by the manuscript to the already published scientific literature

The manuscript explores, for the first time in the Republic of Moldova, the impact of various risk factors on hemostasis dysregulation in patients with non-Hodgkin lymphoma.

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignant lymphoid tumors [1, 2] and is one of the most common malignant lymphoproliferative disorders [3]. According to the results of the GLOBOCAN 2020 study, the incidence of new NHL cases is expected to increase from approximately 544,000 in 2020 to 778,000 by 2040, representing an estimated increase of 43% over two decades [4]. The 5-year prevalence rate of NHL in the Republic of Moldova is approximately 21 cases per 100,000 population [5]. Patients with NHL are prone to develop venous thromboembolism (VTE), which is the second leading cause of mortality among them [6]. In particular, the risk of VTE is further increased in patients undergoing chemotherapy [7]. VTE is induced by the complex interaction of various factors with endogenous or exogenous procoagulant action. [8-10]. It is indisputable that the risk of VTE increases according to the totality of risk factors assessed directly in each individual patient on basis on age, gender, comorbidities, Eastern Cooperative Oncology Group (ECOG), and congenital and acquired thrombophilia [10]. Hemostasis disorders associated with NHL develop severe complications, limit treatment options and their results, and alter quality of life [11, 12]. It is difficult, but absolutely necessary, to predict the risk of thrombosis in asymptomatic carriers of anticardiolipin (aCL), anti-β2-glycoprotein I (anti-β2GP I), and lupus anticoagulant (LA) antibodies, and risk stratification is a fundamental element of current medical research, including in patients with NHL [13]. Seropositivity of these antibodies in malignancies could remain asymptomatic.

As personalized treatment of NHL based on new molecules continues to improve survival rates, there is an urgent need to address the associated risks of thrombosis and bleeding. Assessing the risk of developing hemostatic disorders and subsequent stratification with individual customization for each patient with NHL is absolutely necessary.

The aim of this study was to evaluate the incidence of hemostatic disorders according to age, gender, NHL type, degree of dissemination, B symptoms, disease onset, tumor size, positivity of aCL, anti-β2GP I and LA antibodies, fibrinogen level, LDH and ECOG performance status.

Material and methods

Within the Oncology Institute of the Republic of Moldova conducted the prospective, descriptive study (2020-2024) with the inclusion of 161 de novo patients with aggressive (56.5%) and indolent (43.5%) NHL. The research protocol, information, and acceptance forms were approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (no. 32 of 28.01.2020). The scientific research was conducted with the support of the National Agency for Research and Development, within the Postdoctoral Programs, project number 24.00208.8007.02/PD.

The inclusion criteria were: age over 18 years, an immunohistochemically confirmed diagnosis of NHL, the patient's consent to participate in the study, and the possibility of dynamic monitoring. The respondents were comprehensively evaluated using clinical, paraclinical, and imaging methods to assess the NHL type, stage, onset of the disease (nodal/extranodal), tumor size, and B symptoms. aCL IgM and IgG, anti-β2GP I IgM and IgG antibodies were measured by enzyme-linked immunosorbent assay (ELISA), and LA by the turbidimetry method. Quantitative testing of D-dimers was performed by automatic latex agglutination with photometric detection, with reference values of <0.5 μg/mL. Plasma fibrinogen levels were assessed by coagulometry, with reference values of 200-400 mg/dL (2.0-4.0 g/L). LDH was assessed by spectrophotometric method.

The development and location of thromboses were confirmed by radiological evidence, including venous ultrasonography, computed tomography, or conventional angiography, depending on the anatomical location.

To achieve the proposed goal, the database of the accumulated material was statistically processed using Microsoft Excel, GraphPad Prism ver. 9.3.0, Epi Info 7.2, EpiMax Table, and IBM SPSS Statistics version 26.0. The Mann-Whitney U test was used to compare 2 groups without assuming that the studied values were normally distributed, using the null hypothesis that the medians of two samples were identical. Multiple regression and logistic regression were applied by calculating the odds ratio (OR) and the 95% confidence interval (CI).

Results

According to the eligibility criteria, 161 patients with NHL were included in the study: 84 (52%) men (95% CI, 44-60) and 77 (48%) women (95% CI, 40-56), aged between 24 and 82 years, with a median age of 59 years. In our study, patients with aggressive NHL (91; 56.5%; 95% CI, 48-64) predominated over those with indolent NHL (70; 43.5%; 95% CI, 36-52), with a higher prevalence of advanced stages (III and IV) in 106 cases (65.8%; 95% CI, 58-73) ($p < 0.001$) and B symptoms in 50.3% of cases (95% CI, 42–58) ($p = 0.5$). Extranodal onset in aggressive NHL had approximately the same frequency as in indolent NHL: 33 cases (20.5%; 95% CI, 15-28) versus 37 cases (23%; 95% CI, 17-30) ($p = 0.035$).

Table 1. Characteristics of the research group

Parameter	Patients (n, %, 95% CI)
Age range (years)	24-82
Gender	
Women	77 (48%) (95% CI, 40-56)
Men	84 (52%) (95% CI, 44-60)
Types of NHL	
Aggressive	91 (56.5%) (95% CI, 48-64)
Indolent	70 (43.5%) (95% CI, 36-52)
Cell substrate	
B	157 (97.5%) (95% CI, 93-99)
T	4 (2.5%) (95% CI, 0.80-6.6)
NHL stage	
Localized (I-II)	55 (34.2%) (95% CI, 27-42)
Advanced (III-IV)	106 (65.8%) (95% CI, 58-73)
Symptoms	
A	80 (49.7%), (95% CI, 42-58)
B	81 (50.3%), (95% CI, 42-58)
Onset of the disease	
Nodal	91 (56.5%) (95% CI, 49-64)
Extranodal	70 (43.5%) (95% CI, 36-52)

Note: NHL - non-Hodgkin lymphoma, CI - confidence interval.

Hemostatic disorders were identified in 17 patients (10.6%) (95% CI, 6.3%-16%), with thrombotic events occurring in 11 (6.7%) (95% CI, 3.5%-12%) ($p = 0.12$), compared to 6 (3.9%) (95% CI, 1.4%-8%) hemorrhagic events, in a ratio of 1.8:1. All thrombotic events observed exclusively in the venous system, affecting patients with aggressive NHL in 9 cases (4.3%), (95% CI, 3%-10%) versus patients with indolent NHL in 2 cases (1.6%) (95% CI, 0.2%-4.4%), with a ratio of 4.5:1. The relative risk (RR) was 1.5, and the Odds Ratio (OR) was 3.7; however, the difference did not reach statistical significance in this study (Fisher's exact test, $p = 0.11$).

Venous thromboembolism occurred in the deep veins of the lower extremities in 4 cases (2.4%) (95% CI, 0.7%-6.2%), in the jugular vein in 4 cases (2.4%) (95% CI, 0.7%-6.2%), in the deep veins of the upper extremities in 1 case (0.6%) (95% CI, 0.02%-3.4%), in the portal vein in 1 case (0.6%) (95% CI, 0.02%-3.4%), and in subclavian vein in 1 case (0.6%) (95% CI, 0.02%-3.4%).

VTE was more frequent in men–9 cases (82%) (95% CI, 48%-97%)–compared to women–2 cases (18%) (95% CI, 8%-19%) ($p = 0.041$). This finding suggests that the male gender could be considered a risk factor for thrombosis.

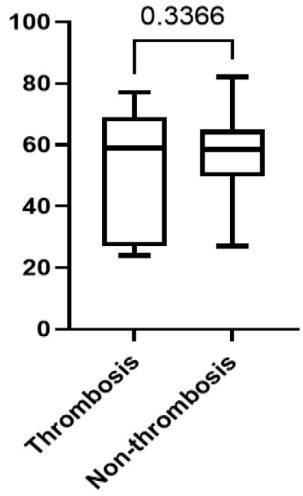

Fig. 1 Distribution of NHL patients according to age and the presence or absence of thrombosis.

The age of NHL patients who developed thrombotic complications ranged from 24 to 77 years, with a mean age of 50 years, whereas the age of non-thrombotic NHL patients ranged from 27 to 79 years, with a mean age of 57 years ($p = 0.3366$) (Fig. 1).

The average interval between thrombosis and the diagnosis of NHL was 3-4 weeks in 7 (4.3%) (95% CI, 1.8%-8.8%) cases. In 4 (2.4%) (95% CI, 0.7%-6.2%) NHL patients, a thrombotic event developed during first-line treatment, with an average onset of 9 months.

Positivity for aCL, anti-β2GPI, and LA antibodies was recorded in 26 patients with B-cell NHL, accounting for 16.2% (95% CI, 10.8%-23%) of cases. Single positivity was observed in 23 (14.3%) (95% CI, 9.3%-21%) cases, double positivity in 2 (1.3%) (95% CI, 0.2%-4.4%) cases, and triple positivity in 1 (0.6%) (95% CI, 0.02%-3.4%) case. Double positivity was represented by the combinations aCL IgM + LA and aCL IgM + anti-β2GPI IgM. Triple positivity was characterized by the association of aCL IgM + LA + anti-β2GPI IgG.

Only 6 (3.7%) (95% CI, 1.4%-8%) of the patients who developed thrombotic complications tested positive for aCL, anti-β2GPI, and LA antibodies. Among the 11 (6.7%) (95% CI, 3.5%-12%) NHL patients with thrombosis, 3 (1.8%) (95% CI, 0.4%-5.4%) had single antibody positivity (2 with LA and 1 with anti-β2GPI IgM); 2 (1.3%) (95% CI, 0.2%-4.4%) had double antibody positivity (aCL IgM + LA and aCL IgM + anti-β2GPI IgM); and 1 (0.6%), (95% CI, 0.02%-3.4%) had triple antibody positivity (LA + aCL IgM + anti-β2GPI IgG).

The primary involvement of mediastinal nodes in patients who developed thrombosis was 45.5%, compared to non-mediastinal involvement in 54.6%. In contrast, among patients with NHL without thrombosis, mediastinal node involvement was observed in 12.5%, while non-mediastinal involvement was seen in 76%. These results were statistically significant with a p-value of 0.02, as assessed by the Fisher exact test. The relative risk (RR) of thrombosis association is 1.3 (95% CI, 1.04%-1.98%), and the Odds Ratio (OR) is 5.069 (95% CI, 0.34%-16.8%).

Nodal tumor sizes ≥ 7 cm were predominant in 8 (4.9%) (95% CI, 2.2%-10%) cases out of 11 (6.7%) (95% CI, 3.5%-12%) NHL patients with associated VTE, although the difference did not reach statistical significance (Fisher exact test,

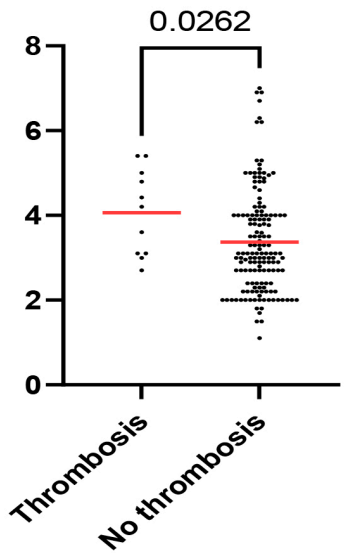

Fig. 2 Scatter plot of fibrinogen levels across patients with and without thrombotic events. P-value shown for the Mann-Whitney U test.

p = 0.1). Among these, 6 (3.7%) (95% CI, 1.4%-8%) patients had Diffuse large B-cell lymphoma, and 1 (0.6%) (95% CI, 0.02%-3.4%) patient had NHL of gray zone cells, and 1 (0.6%) (95% CI, 0.02%-3.4%) patient had small lymphocytic lymphoma.

No statistical difference was found between cases with and without thrombosis regarding LDH levels (p = 0.69, Mann-Whitney U test).

A high level of fibrinogen was found in 39 (24.4%) (95% CI, 18%-32%) patients: 30 (18.8%) (95% CI, 13%-26%) cases in aggressive NHL and 9 (5.6%) (95% CI, 3%-10%) cases in indolent NHL, with a ratio of 3.3:1. Notably, patients with a confirmed thrombotic event had a higher level of fibrinogen at diagnosis (median, 4.2; mean, 4.06; 95% CI of mean, 3.4%-4.7%) compared to those who did not manifest thrombotic events (median, 3.1; mean, 3.4; 95% CI of mean, 3.1%-3.5%), suggesting a potential association between fibrinogen levels at diagnosis and the risk of thrombosis in lymphoma patients (Mann-Whitney U test, p = 0.02) (Fig. 2).

The analysis of the distribution of patients according to the level of D-dimers and subtype of NHL reveals high values (≥ 501 ng/ml) in 45 patients (28%) (95% CI, 21%-36%), including those with aggressive NHL – 31 cases (19.3%) (95% CI, 13%-26%) and indolent NHL – 14 cases (8.7%) (95% CI, 3%-10%) (p = 0.0015, Mann-Whitney U test).

The distribution of patients with NHL and VTE according to ECOG performance status shows an ECOG score of 2-4 in 7 patients (4.2%) (95% CI, 1.8%-8.8%) and an ECOG score of 0-1 in 4 patients (2.5%) (95% CI, 0.7%-6.2%). Statistical significance was not reached in the thrombosis analysis according to ECOG (p = 0.1, Fisher's exact test).

Discussion

The current maximally personalized treatment of NHL allows for life prolongation and even cure; however, complications associated with the disease and treatment methodology inevitably have a major impact on quality of life. Among these complications are hemostasis disorders, which limit treatment options and negatively affect patients' quality of life [11, 12].

A meta-analysis conducted by Caruso and colleagues indicated that the overall incidence rate of thrombosis in non-Hodgkin lymphoma patients is 6.4% [14]. A similar result was obtained in our study, with thrombotic events found in 6.7% of cases. According to the research results by Hohaus and colleagues, aggressive NHL is more often associated with thrombotic complications than indolent NHL, with VTE occurring in 10-15% of cases within the first year of diagnosis [15]. Similar conclusions were drawn from our research, which found thrombosis in 4.3% of aggressive NHL cases compared to 1.6% of indolent NHL cases.

An American study analyzed data from 16,755 patients with aggressive and indolent NHL and found that age over 45 years at baseline is already a risk factor for VTE in NHL patients [16]. The average age of patients in our study who developed NHL-associated thrombosis was 50 years, which does not significantly differ from the findings of other studies.

Female gender as a potential risk factor for severe grade III VTE was assessed in a multicenter study conducted in Italian hematology clinics [17]. In our study, we obtained different results: VTE developed more often in men (82%) than in women (18%) (p = 0.041), suggesting that male gender may be considered a risk factor for thrombosis.

Retrospective studies analyzed and described by Razak demonstrate differences in both gender and thrombosis type (arterial vs venous). According to the authors, women are at higher risk of venous thromboembolism, while men are more susceptible to arterial thromboembolism [18]. In our study, thrombotic events were assessed only in the venous system.

The location and size of the tumor in NHL increase the risk of thrombotic events through external compression of large blood vessels. Serbian researchers found that mediastinal and extranodal lymphoma onset are major risk factors for thromboembolism [19]. According to Yuen's findings, mediastinal involvement was associated with an eightfold higher risk of VTE, while extranodal locations, such as the central nervous system, testis, and gastrointestinal tract, increased the risk of VTE by 2.3-fold [20]. In our study, primary mediastinal nodes involvement was observed in 45.5% of patients who developed thrombosis, compared to 54.6% cases with non-mediastinal involvement. Among NHL patients without thrombosis, mediastinal involvement was observed in 12.5% compared to 76% with non-mediastinal involvement. These results were statistically significant (p = 0.02, Fisher's exact test).

The risk of VTE is elevated during the first two months after lymphoma diagnosis and decreases over time [15]. Similar results were reported in a prospective Spanish study, where VTE developed within the first 90 days after diagnosis and initiation of antitumor therapy in 9.5% of patients with malignant lymphomas and multiple myeloma [21]. In our study, thrombotic complications occurred between 3-4 weeks in 4.3% of cases to 9 months in 2.4% of cases.

According to Barreno-Rocha, the synthesis of phospholipid antibodies by tumor cells serves as a target for aCL, LA, and anti-β2GPI [22]. In the global population, the prevalence of aPL antibodies varies between 1-5% and increases with chronic inflammatory and infectious diseases, as well as with the development of oncological conditions [23, 24].

Our study demonstrates a 16.2% incidence of aCL, LA, and anti-β2GPI antibodies in newly diagnosed NHL patients. A lower prevalence of autoantibodies–9 (41%) in NHL patients–was reported by Sciarra et al. in 1995 [25]. In our cohort, LA was the most prevalent, being positive in 21 (13.1%) cases, followed by anti-β2GPI IgM and aCL IgM antibodies, each found in 4 (2.5%) cases. A higher prevalence (40%) of anti-β2GPI IgM was reported among 86 NHL patients treated at the Institute of Hematology in Israel [26].

A major risk for thrombosis is suspected not only when an individual antibody is detected but also when an association of 2-3 antibody types is present, regardless of their IgG or IgM isotype. This is referred to as the "aPL double profile" and "aPL triple profile", respectively [27].

Niimi and colleagues aimed to assess the clinical utility of increasing the D-dimer cut-off value by evaluating this parameter in 208 patients with malignancies, including those with NHL. The study results highlighted an optimal cut-off value of 4.0 μg/mL for the diagnosis of DVT in patients with malignancy. Additionally, the study suggested that combining the Khorana score with D-dimer levels provided a more accurate diagnosis of DVT than the Khorana score alone [28].

A decrease in ECOG performance status (2-4) was associated with a more proximal localization of VTE, particularly in the lower limbs [29]. This relationship between low ECOG performance status and thrombosis was confirmed in a study conducted by Hohaus. In our study, the distribution of NHL patients with VTE according to ECOG performance status showed a higher prevalence of ECOG 2-4 in 7 (4.2%) cases compared to ECOG 0-1 in 4 (2.5%) cases.

Focusing on these antibodies could lead to better management of NHL patients by aiding in prediction, ultimately improving overall survival and quality of life.

Conclusions

These differences suggest that not all seropositive NHL subjects develop thrombosis, and it is possible that some NHL patients with thrombosis are seronegative for aCL, anti-β2GPI, and LA antibodies. Patients with tumor conglomerates ≥ 7 cm, regardless of aCL, anti-β2GPI, and LA antibody positivity, but with mediastinal localization, present the highest risk of developing thrombotic complications.

The prevalence of aCL, anti-β2GPI, and LA antibodies in NHL patients was appreciated in 16.2% of cases. This is expressed as single-positivity in 14.3%, double positivity in 1.3%, and triple positivity in 0.6%, exclusively in B-cell NHL. A statistically significant difference in antibody positivity was observed based on age and NHL type. However, antibody synthesis in NHL patients showed no statistically significant association with gender, disease dissemination, B symptoms, or the location of the primary tumor focus. The risk of VTE in NHL is influenced by gender, NHL type, tumor size, mediastinal onset, hyperfibrinogenemia, antibody synthesis. However, no statistically significant association was found between VTE occurrence in NHL patients and disease stage, B symptoms, LDH levels or ECOG performance status.

Competing interests

None declared.

Authors' contributions

SB and MM played a crucial role in the collection and analysis of empirical data, laying the foundation for the central argument of the paper. Their meticulous work enabled not only a novel interpretation of the data but also its integration into the broader context of specialist research. All authors have read and approved the final version of the manuscript.

Ethics approval

The study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes No. 32, dated 28.01.2020).

Patient consent

Obtained.

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RESEARCH ARTICLE

Development of a mathematical model for thrombosis risk prediction using serum biomarkers

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ABSTRACT

Introduction. Thrombosis is a frequently underdiagnosed condition associated with high mortality in neglected cases. Many factors, including geoheliophysical and biochemical ones, are responsible for thrombosis modulation. Routine investigations may sometimes be inconsistent and, thus, unreliable in a clinical setting.

Material and methods. Data were collected from patients treated in the Department of Vascular Surgery at the 'Timofei Moșneaga' Republican Clinical Hospital, Chișinău, Republic of Moldova. A total of 1,865 patients were initially included in the study. After applying rigorous inclusion and exclusion criteria, 263 eligible patients were identified, and their complete blood counts and biochemical reports were retrospectively analyzed.

Results. The analysis revealed increased mean values for absolute polymorphonuclear neutrophils, absolute monocytes, erythrocyte sedimentation rate (ESR), and glucose. The median values of these indicators, except for absolute polymorphonuclear neutrophils and ESR in female patients, were also elevated above normal ranges. Significant Pearson and Spearman correlations were identified among the analyzed indicators, and a binary logistic regression model was constructed using the most statistically significant variables.

Discussion. Usual mathematical models that outline thrombosis consider deep vein thrombosis without a sustainable arterial assessment. The sensitivity of our model is lower than that of the D-dimer, while the specificity is almost the same. Platelets and clotting tests are well-known, reliable indicators; however, novel contemporary augmentations to these may, in turn, increase the predictive capability of our model if applied. This study has its limitations due to the lack of variance in the variance inflation factors (VIF), preventing the evaluation of multicollinearity among the included biomarkers.

Conclusions. The mathematical model developed in this study shows potential for further clinical application; however, additional research, validation, and the incorporation of non-biochemical indicators may be necessary to enhance its predictive accuracy.

Keywords: thrombosis, biomarkers, models, theoretical.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

There are no mathematical models that can accurately predict thrombosis risk in a clinical setting; thus, the development of one is a mainstay task.

The research hypothesis

There are certain biomarkers that may be used to develop a mathematical model capable of predicting thrombosis risk.

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The novelty added by the manuscript to the already published scientific literature

The development of a new mathematical model that may become more reliable and sustainable over time.

Introduction

Thrombosis is defined as the formation of a blood clot that can obstruct the normal permeability of the circulatory system [1]. The mortality burden associated with thromboembolic events is substantial (25% fatal outcomes) [2].

Differences in thrombosis rates across regions are thought to be influenced by variations in plasma rheology and clotting factors, such as fibrinogen, and factor VII, which could potentially overshadow the impact of seasonality [3]. The interactions of the endocrine system and its array of pathologies are of utmost importance when considering the etiology of thrombosis. Conditions like hyperthyroidism, hypercortisolism (endogenous or exogenous), growth hormone excess, hyperprolactinemia, and pregnancy, which involve direct or indirect involvement of the hormonal system, are known to have a higher incidence of thrombosis [4].

In the past, erythrocytes were considered to play a passive role in thrombotic events. However, they are now recognized as active contributors. Erythrocytes can enhance blood viscosity, interact with vessel walls, and influence the spatial organization of platelets during aggregation [5]. This aggregation, a critical process in thrombosis, is driven by elevated levels of adenosine diphosphate (ADP) [6]. Leukocytes, especially monocytes, are renowned for their capacity to promote clot formation in an environment that has the components required for thrombosis to emerge [7]. Serum bilirubin has remarkable antioxidative and cytoprotective effects [8], which in turn warrants that its low concentrations will lead to increased venous thromboembolism events in an acute respiratory infection setting [9-10].

Routine hemoleukogram, which measures parameters such as red blood cell count, white blood cell count, and hemoglobin levels, remains a valuable tool in the assessment of deep vein thrombosis (DVT). These routine measurements are essential for identifying patients at risk of pre-thrombotic or thrombotic conditions [11]. While advanced biomarkers, including D-dimers, selectins, microparticles, and inflammatory cytokines, demonstrate high accuracy in thrombosis evaluation, their utilization is often restricted to private healthcare settings due to their high cost. This financial barrier poses significant challenges for many healthcare systems globally, limiting the accessibility of these biomarkers in routine clinical practice [12].

Current mathematical models for assessing thrombosis risk, such as the Wells score, demonstrate limited performance. Their efficiency varies significantly, ranging from 0.5% to 23.4%, depending on the expertise of the specialist applying the model [13]. Additionally, these models perform poorly in critically ill patients, further limiting their reliability in high-risk populations [14].

The aim of this study was to develop a mathematical model for thrombosis diagnosis using serum biomarkers, particularly in patients lacking imaging data.

Material and methods

Study population. The study was conducted in the Department of Vascular Surgery at the *Timofei Moșneaga* Republican Clinical Hospital (RCH) in Chișinău, Republic of Moldova. In 2019, a total of 1,865 patients were admitted to the department for various vascular conditions, including atherosclerosis, atherothrombosis, thrombosis, and thromboembolism. The department primarily relies on a combination of biochemical laboratory investigations and imaging studies as the cornerstone of its clinical research and diagnostic methodologies.

Inclusion and exclusion criteria. To minimize systemic bias, reduce the risk of incomplete data inputs, and ensure consistency in data collection, stringent inclusion and exclusion criteria were established for the study population. Only patients who underwent a complete blood count (CBC) and biochemical investigation during the inpatient stage (on the first day of hospital admission) and tested negative for methicillin-resistant *Staphylococcus* (MRS) antibodies were included. A comprehensive range of comorbidities and conditions were considered exclusion criteria to ensure the reliability and objectivity of the biochemical results. The excluded conditions included hepatic and splenic disorders, oncological and infectious conditions, hematological disorders, autoimmune and dermatological conditions, vascular and cardiac conditions, gastrointestinal and endocrine disorders, and additional exclusions such as trauma, open wounds, systemic diseases requiring artificial grafts or stoma implants, post-thrombotic or post-inflammatory syndromes, chronic obstructive pulmonary disease (COPD), and patients receiving anticoagulant therapy. The exclusion criteria were carefully designed to reduce confounding variables and ensure high-quality biochemical data. It should be mentioned that the controls were confirmed to be patients who did not have thrombosis, using the same investigations as the patients with confirmed thrombosis (imaging and laboratory methods).

Statistical Data. A total of 263 patients included in the final study cohort were systematically documented and organized using Microsoft® Excel® 2013 (15.0.4569.1504). The data were collected retrospectively. The dataset encompassed a broad range of demographic, clinical, and laboratory parameters, including: demographic information (age, gender); clinical features (affected limb region: upper or lower limbs, type of thrombosis: arterial or venous, and season of occurrence); hematological parameters (white blood cell count [WBC], red blood cell count [RBC], hemoglobin

[HGB], hematocrit [HCT], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelet count [PLT], red cell distribution width – coefficient of variation [RDW-CV], and differential counts [absolute and relative values] of neutrophils, lymphocytes, monocytes, eosinophils, and basophils); inflammatory markers (erythrocyte sedimentation rate [ESR]; biochemical parameters (urea, aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], creatinine, total bilirubin, conjugated bilirubin, unconjugated bilirubin, glucose, albumin, and total protein); coagulation profiles (Quick prothrombin, international normalized ratio [INR], fibrinogen levels, activated partial thromboplastin time [aPTT], and thrombin time [TT]. This comprehensive collection of variables ensured a robust dataset for the subsequent analysis, enabling a thorough investigation of potential associations between the data.

Statistical Methods. The data were analyzed using IBM SPSS Statistics (version 26.0.0.0). The Shapiro-Wilk and Kolmogorov-Smirnov tests were applied to assess the normality of the data distribution. For normally distributed data, a one-sample t-test was performed with a t-value of 1.97 and a 95% confidence interval (CI). For non-normally distributed data, the one-sample Wilcoxon signed-rank test was utilized. Descriptive statistics, including mean values, standard deviations, medians, and minimum and maximum values, were calculated to summarize the data. Pearson and Spearman correlation coefficients were determined to evaluate relationships between the studied variables. Binary logistic regression analysis was conducted to identify, using mathematical methods, biochemical markers with potential predictive value for thrombosis events. An algorithm was developed using the statistically significant biomarkers identified in the analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results

The mean age of the patients was 59.21±13.50 years while the median was 62 years, ranging in the interval of 23-90 years. Based on gender distribution, the study included 164 male patients (62.4%) and 99 female patients (37.6%). Among these, 74 patients (28.1%) presented during the winter season, 57 (21.7%) during spring, 72 (27.4%) during autumn, and 60 (22.8%) during summer. Of the total participants, 143 patients had thrombosis, while 120 served as controls.

In 125 cases (87.41%), the lower limbs were affected, whereas the upper limbs were affected in 18 cases (12.59%). Regarding vascular involvement, the arterial system was implicated in 63 cases (44.06%), while the venous system was affected in 80 cases (55.94%).

The Shapiro-Wilk and Kolmogorov-Smirnov tests demonstrated that the data followed a normal distribution, except for hematocrit, relative polymorphonucleated neutrophils, and relative lymphocytes.

The one-sample t-test indicated that all parameters, except for relative eosinophils and conjugated bilirubin, were statistically significant, with n = 263, t = 1.97, and a 95% confidence interval (CI). The one-sample Wilcoxon signed-rank test was applied to relative eosinophils, where the sample median (MDN = 1.40) differed from the hypothesized population median (2.5), n = 263, Z = -7.818, 95% CI, r = 0.482. Similarly, the test for conjugated bilirubin demonstrated a sample median (MDN = 0) differing from the hypothesized population median (3.0), n = 263, Z = -8.432, 95% CI, r = 0.519, confirming their statistical significance.

Mean values for absolute polymorphonucleated neutrophils, absolute monocytes, erythrocyte sedimentation rate (ESR) in both male and female patients, and glucose were elevated above normal values (Table 1). Additionally, the median values for absolute monocytes, ESR in male patients, and glucose were also above normal values (Table 1).

The strongest Pearson and Spearman correlations (Table 2) are detailed. It is important to note that these values do not necessarily reflect the patient's condition during thrombosis events or in controls. Instead, they aim to identify potential bias factors in the diagnostic process. While such elevations are commonly associated with pathological states, they do not appear to directly correlate with the severity of the condition.

Table 1. Indicators above normal statistical values

Indicator	Mean±SD	Median value	Minimum	Maximum	Normal range
NEUT#	5.35±2.43	4.88	1.45	20.11	2-5 x 10^3/µL
MONO#	0.69±0.52	0.63	0.17	7.7	0.09-0.6 x 10^3/µL
ESR_{total}	16.87±28.89	12	1	445	2-10 mm/h
$ESR_{male\ gender}$	17.89±35.45	12	1	445	2-10 mm/h
$ESR_{female\ gender}$	15.19±11.72	12	2	65	3-12 mm/h
Glucose	5.98±2.07	5.6	1.47	20.71	3.5-5.5 mM/L

Note: NEUT# – absolute polymorphonucleated neutrophils; MONO# – absolute monocytes; ESR – erythrocyte sedimentation rate; SD – standard deviation.

Considering the statistical significance of the b-values derived from the binary logistic regression model and the predictive capability for thrombosis events, as indicated by a Nagelkerke R^2 value of 0.203, a mathematical model has been developed. This model includes a constant and the following statistically significant variables: platelets (PLT), mean platelet volume (MPV), and thrombin time (TT). The following mathematical model may be applied:

$$b = 4.854 - 0.009\ x\ PLT - 0.461\ x\ MPV + 0.096\ x\ TT\ .$$

Once the b-values are determined, the thrombosis chance (TC) is calculated using the following formula: $TC = \frac{e^b}{1+e^b}$.

The specificity of this model was 55.8%, while its sensitivity was 76.9%. The negative predictive value (NPV) was 67%, and the positive predictive value (PPV) was 67.48%.

Table 2. Pearson and Spearman correlations between the biochemical markers

Pearson correlations	Value	Spearman correlations	Value
NEUT% x LYMPH%	-0.950**	NEUT% x LYMPH%	-0.952**
NEUT# x LYMPH%	-0.644**	QP x INR	-0.923**
QP x INR	-0.617**	NEUT# x LYMPH%	-0.671**
MCH x RDW-CV	-0.540**	NEUT# x BASO%	-0.542**
NEUT% x LYMPH#	-0.476**	NEUT% x BASO%	-0.516**
BASO# x BASO%	0.766*	HGB x HCT	0.831**
RBC x HCT	0.803**	RBC x HCT	0.838**
EO# x EO%	0.883**	EO# x EO%	0.908**
TotalBil x UnconjBil	0.909**	TotalBil x UnconjBil	0.919**
WBC x NEUT#	0.942**	WBC x NEUT#	0.935**

Note: * Statistical significance at $p < 0.05$; ** Statistical significance at $p<0.01$; NEUT% – relative polymorphonucleated neutrophils; LYMPH% – relative lymphocytes; BASO% – relative polymorphonucleated basophils; EO% – relative polymorphonucleated eosinophils; NEUT# – absolute polymorphonucleated neutrophils; LYMPH# – absolute lymphocytes; BASO# – absolute polymorphonucleated basophils; EO# – absolute polymorphonucleated eosinophils; RBC – red blood cells; WBC – white blood cells; HGB – hemoglobin; HCT – hematocrit; QP – Quick prothrombin; INR – international normalized ratio; MCH – mean corpuscular hemoglobin; RDW-CV – red cell distribution width (coefficient of variation); TotalBil – total bilirubin; UnconjBil – unconjugated bilirubin

Discussion

Previous models for thrombosis evaluation were primarily developed to assess deep vein thrombosis (affecting the upper or lower limbs) and pulmonary embolism, without adequately addressing arterial thrombosis [15-17]. In this research, a new model has been proposed that integrates both arterial and venous thrombosis, providing a comprehensive framework for the empirical management of patients. The proposed model relies on widely available and inexpensive biomarkers, making it particularly suitable for resource-limited settings where advanced imaging or specialized tests are not accessible. However, its specificity (55.8%) limits its standalone utility in clinical practice.

The widely used screening test of D-dimers has a high incidence of false-positive results due to its low specificity. As a result, its application may introduce a significant range of systematic errors, despite its clinical utility [18]. Our score is generally less sensitive than D-dimers; however, given their similar specificity, it could serve as an additional confirmatory tool for patients who cannot undergo this test.

Elevated absolute polymorphonucleated basophil values have been associated with increased mortality in patients with coronary artery disease (CAD), suggesting their potential role as a pro-thrombotic marker [19].

Platelets, the primary circulating elements responsible for clot formation [20], are expected to fluctuate during thrombosis events, reflecting their critical role in the coagulation process.

Although platelets are the key players in primary hemostasis, they can also contribute to secondary hemostasis through mediators found in their granules, including alpha, dense, and lysosomal granules. Additionally, cytosolic factors can sustain the coagulation cascade, further enhancing biochemical interactions at this level [21]. These molecules may serve as potential predictive biomarkers for future algorithm development [22-23].

Mean platelet volume (MPV) has been shown to reduce thrombosis risk in multiple regression analysis, consistent with the findings of this study [24]. However, this contrasts with classical high-evidence studies that identify elevated mean platelet volume as a risk factor for thrombosis [25]. MPV has been found to have low significance in predicting thrombosis in COVID-19 patients [26], while demonstrating good sensitivity and specificity in assessing thrombosis recurrence in conditions such as antiphospholipid syndrome (APS) [27]. However, in a retrospective study, MPV was found to be less effective compared to D-dimers [28].

Thrombin time (TT) reflects the ability of fibrinogen to convert into fibrin. An elevated TT may indicate fibrinogen deficiency, dysfunction, or disruption of other coagulation factors [29]. A study conducted in Japan states that TT, when enhanced by clot waveform analysis (CWA), may provide valuable insights into hemostatic abnormalities in patients without deficiencies in other clotting components [30]. This novel global coagulation assessment tool may also mitigate the influence of certain drugs due to its biophysical nature [31-32]. However, both activated partial thromboplastin time (aPTT) and TT are known for their inherent variability and limited diagnostic utility in thrombotic events. Individually assessed biomarkers are often deemed unreliable in thrombosis diagnosis [33]. A significant portion of false-negative results may be attributed to the depletion of key thrombogenic elements–platelets, fibrinogen/fibrin, protein C, and protein S–which directly impact Quick prothrombin (PT) and aPTT [34]. Notably, a widely recognized scoring system requires platelet count, D-dimer levels, PT, and fibrinogen values to predict the onset of disseminated intravascular coagulation (DIC) [35].

It can be hypothesized that enhancing current standard methods for thrombosis assessment may improve the specificity and sensitivity of the proposed mathematical model. However, this study did not evaluate variance inflation factors (VIF) to assess multicollinearity among the included biomarkers.

Conclusions

This study proposes a simple and cost-effective model for thrombosis risk prediction based on platelets, MPV, and thrombin time. While the model shows promise for clinical application, further validation, refinement, and the integration of advanced biomarkers are needed to enhance its predictive accuracy and clinical applicability.

Competing interest

None declared.

Contribution of authors

DC designed the study, collected, and analyzed the data. IT critically revised the manuscript and analyzed the data. EP critically evaluated the results and assessed their applicability. OA designed the protocol for patient' eligibility. EC critically revised the manuscript.

Ethics approval

No approval was required for this study.

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RESEARCH ARTICLE

Exploring knowledge and perceptions of domestic violence among medical students and physicians in the Republic of Moldova

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ABSTRACT

Introduction. Domestic violence is one of the most widespread human rights violations in the world. The health sector plays a vital role in preventing domestic violence, helping to identify abuse early, providing victims with the necessary treatment, and referring them to appropriate care. The paper aims to explore the level of knowledge and perceptions in the field of domestic violence among current and future physicians in the Republic of Moldova, in order to assess their educational needs.

Materials and methods. In order to achieve this goal, an observational, descriptive, cross-sectional study based on a survey of 832 medical students, residents, and doctors from *Nicolae Testemițanu* State University of Medicine and Pharmacy and medical institutions from the Republic of Moldova was performed. For this purpose, a confidential questionnaire focused on assessing the level of medical staff's knowledge, perceptions, and attitudes in the field of domestic violence was used.

Results. The study results highlight the limited knowledge of the respondents about concept of domestic violence, its forms, the role and distinct elements of the health system's response to such cases, reporting duties, vulnerable groups of victims, and their legal protection measures. Only 21.5% of respondents were able to identify all the characteristics and the definition of domestic violence, 7.4% recognized all forms of violence, 10.9% were able to outline legal protection measures, and 33.8% were able to recognize cases where reporting to law enforcement is mandatory. The analysis of perceptions showed that medical respondents are still influenced by some stereotypes regarding the roles of men and women in society–similar to other members of society, though to a lesser extent.

Conclusions. Current and future medical doctors in the Republic of Moldova strongly need to be trained in order to strengthen their capacity to adequately respond to cases of domestic violence. The study results can be used as evidence-based proposals for enriching existing training programs or designing new ones to support healthcare practitioners in the proper management of domestic violence cases.

Keywords: domestic violence, knowledge and perceptions, medical students, doctors.

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Key messages

What is not known yet about the issue addressed in the submitted manuscript

While the health system is recognized as a key authority in combating domestic violence, there is a lack of research assessing the knowledge, perceptions, and attitudes of current and future medical professionals in the Republic of Moldova. Specific gaps include medical staff's understanding of domestic violence concepts, their ability to identify abuse, their awareness of legal protection measures, and the extent to which societal stereotypes influence their responses.

The research hypothesis

Medical professionals and students in the Republic of Moldova have significant gaps in knowledge, perceptions, and attitudes regarding domestic violence, which affect their ability to adequately identify, respond to, and support victims.

The novelty added to the scientific literature in the field

This study offers a unique understanding of the educational gaps and training needs of medical professionals in the Republic of Moldova regarding domestic violence. It is the only one study in the Republic of Moldova to evaluate how stereotypes, knowledge gaps, and limited legal awareness influence healthcare responses in this context. The findings offer a foundation for designing targeted training programs, contributing to the global effort to strengthen the role of healthcare systems in addressing domestic violence..

Introduction

Domestic violence (DV) is a severe violation of human rights and a significant global public health issue, with its widespread prevalence affecting communities worldwide. DV concepts are understood differently across various cultural, social, and legal contexts [1]. However, the World Health Organization (WHO) definition is one of the most recognized and globally accepted. WHO defines *domestic violence* as *any act of gender-based violence that results in, or is likely to result in, physical, sexual, or mental harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or private life* [2]. On the other hand, the United Nations defines *domestic violence or abuse* as a *pattern of behavior in any relationship that is used to gain or maintain power and control over an intimate partner* [3]. Both international organizations highlight that abuse might be physical, sexual, emotional, economic, or psychological actions or threats of actions that influence another person. The Republic of Moldova's legislation on preventing and combating *domestic violence* defines it as *acts, including threats, of physical, sexual, psychological, spiritual, or economic violence (excluding self-defense actions) committed by a family member against another family member, inflicting material or moral damage upon the victim* [4].

Although domestic violence has been recognized as a social problem for several decades, the extent of this phenomenon continues to have a significant prevalence today [5]. Domestic violence is considered an „unseen crime" that many victims may be too frightened or too ashamed to report [6]. It is therefore difficult, or even impossible, to produce accurate statistics on the true prevalence of this form of violence, as the number of reported instances will be much lower than the number of instances that actually occur [7]. However, globally, it is estimated that nearly one-third (30%) of women who have been in an intimate relationship have experienced some form of physical and/or sexual violence perpetrated by an intimate partner during their lifetime [2]. In some regions of the world, the percentages are even higher: 40.6% in Andean Latin America, 41.8% in West Sub-Saharan Africa, 41.7% in South Asia, and 65.6% in Central Sub-Saharan Africa [8]. According to WHO (2021), younger women are most vulnerable, 27% of women aged 15–49 worldwide have experienced physical and/or sexual violence from their partner [9, 10]. Globally, 81,000 women and girls were killed in 2020, with around 47,000 of them (58%) dying at the hands of an intimate partner or family member, which equates to a woman or girl being killed every 11 minutes in their home [11, 12]. The Council of Europe reports that 45% of women have suffered from some form of violence during their lifetime, and between 12% and 15% of women in Europe over the age of 16 are victims of domestic violence [13]. In the Republic of Moldova, 73% of women have been subjected to at least one form of violence by an intimate partner at some point in their lives, physical violence being attested in 33% of cases, which is much higher than the average rate in the EU [14]. According to the Ministry of Internal Affairs of the Republic of Moldova, in 2022, 2,471 domestic violence cases were detected, with 81.3% of the victims being women [15]. We believe the dynamics of victims' reporting to the police can also reflect the extent of domestic violence. Thus, according to the Ministry of Internal Affairs, there has been a constant increase in the reporting of cases, from 6,569 in 2012 to 15,526 in 2022. It is important to note that in the Republic of Moldova, domestic violence generates about 30 homicides and 5 cases of suicide annually [15].

Domestic violence significantly contributes to the ill health of society, and it is associated with many short- and long-term harmful physical and mental health problems and conditions [16, 17]. It is well known that the health sector plays a vital role in preventing domestic violence by helping to identify abuse early, providing victims with the necessary treatment, and referring them to appropriate care. Health services must be places where victims feel safe, are treated with respect, are not stigmatized, and can receive quality, informed support [18]. A comprehensive health sector response to the problem is needed, particularly in addressing the reluctance of victims to seek help [19]. For many victims, visiting a doctor is the first and often the only step toward accessing necessary medical care. Surveys indicate that women largely trust healthcare providers and consider it acceptable for doctors to ask about acts of violence if they suspect or find injuries on patients' bodies [20]. In this sense, medical professionals are uniquely positioned to intervene in critical situations for women and children who are constantly subjected to acts of violence [21]. The World Health Organization recommends training health practitioners to respond adequately to violence against women [16]. By providing safe and effective, victim-centered care,

appropriately trained health practitioners can help alleviate the health consequences of violence and reduce its recurrence [22, 23]. These actions can have a significant impact on the health and well-being of DV victims, increase their access to high-quality, patient-tailored medical care, and ensure the protection of their rights [24].

Material and methods

An observational, descriptive, cross-sectional study based on a survey of medical students, residents, and doctors from *Nicolae Testemiţanu* State University of Medicine and Pharmacy and medical institutions in the Republic of Moldova was conducted. In order to achieve the study's goal, a confidential questionnaire was designed, focusing on the following elements: the level of knowledge of medical students, resident doctors, and medical practitioners regarding domestic violence and specific elements of the health system's response to these cases, as well as their perceptions of social norms related to the roles of men and women in society and family. The questionnaire was developed in consultation with national partners, including representatives of civil society, specialized central public authorities responsible for preventing and combating domestic violence, and international institutions (World Health Organization, UN Women Moldova, UNFPA).

The questionnaire includes three sections: I) the respondent's demographic characteristics; II) an assessment of the respondent's knowledge in the field of domestic violence; III) an assessment of the respondents' perceptions and attitudes toward domestic violence. It includes 49 questions, of which 43 are closed-ended, 3 are semi closed-ended, and 3 are open-ended, including scaled semantic and control questions. Some of the questions focused on identifying the respondent's opinion and its degree of expression using Likert scales (from 1 to 5).

As a general statistical community, 16,330 medical students and physicians were considered (4,116 students – *Nicolae Testemiţanu* State University of Medicine and Pharmacy data, January 2023; 12,214 physicians – Statistical Yearbook "Public Health in Moldova 2022"). The representative sample was calculated in EpiInfo 7.2.2.6 program, „StatCalc – Sample Size and Power" section, based on the following parameters: a confidence interval for 95.0% significance of the results, a probability of the phenomenon's occurrence of 50.0%, and a design-effect of 2. Since the questionnaires were completed by respondents, to keep the sample representative, the probability of non-response was taken into consideration, which was predicted to be a maximum of 10.0% for the study sample. This resulted in an adjusted sample of 825 respondents, selected according to specific inclusion/exclusion criteria. The structure of the general statistical population was ensured by stratifying the sample according to the respondents' professional status (students – 25.3%, residents/physicians – 74.7%). As a result, the final number of respondents in the representative sample should be at least: students – 209 and residents/physicians – 616.

To make it more convenient to survey respondents, the questionnaire was structured and administered on the Google Forms platform, ensuring unlimited access for potential respondents from across the country and from various specialties. The link to the questionnaire was distributed via email; its completion was voluntary and anonymous. Respondents' consent for completing the questionnaire was obtained. Microsoft Excel 2016 was used to collect the data, and the Statistical Package for the Social Sciences (SPSS) software, ver. 26.0, was used for statistical analysis.

The study is part of the "Medico-legal identification of adult victims of non-lethal physical domestic violence" research conducted at the Department of Forensic Medicine and was approved by the Ethics Committee of Nicolae Testemiţanu State University of Medicine and Pharmacy (Minutes No. 3, May 18, 2023).

Results

I. The respondents' demographic characteristics

The questionnaire was completed by 832 respondents, of whom 214 (25.7%) were students, 96 (11.5%) were residents, and 522 (62.7%) were physicians. In terms of gender, females accounted for 78.2%, males 21.5%, and 0.2% of respondents identified as another gender. In this study, most participants were aged under 35 (386, 46.4%), being students or young professionals. Approximately 32.9% (274) of the total participants fell within the age range of 36-55 years, while only 172 (20.7%) were over 56 years old. Of the respondents, 82.0%studied or worked in rural medical institutions, and only 18.0% in urban ones. The study showed that most respondents had some professional experience: 28.1% had 21-40 years of professional experience, 24.5% had 6-20 years, 20.2% had less than five years, and 7.8% had more than 40 years. The study sample also included respondents with no work experience (19.4%).

An important aspect explored in the study was to find out how often respondents interacted with patients experiencing domestic violence. As a result, more than half of the respondents (64.4%) reported that they occasionally interact with patients who are victims of domestic violence, another 13.2% interact frequently, and only 1.4% interact daily. It is to be mentioned that 20.9% of respondents have never interacted with domestic violence victims during their professional lifetime, because most of them are students.

Within the survey, the respondents were asked to rate their level of knowledge regarding domestic violence and the health system's response to such cases on a scale of 1 to 5. The results revealed that 60.9% of the participants rated their level of knowledge as 1–3.

II. Assessment of the respondent's knowledge in the field of domestic violence

The aim of this section was to assess the level of knowledge and understanding of the domestic violence phenomenon and to identify possible gaps in this field. It consisted of 18 questions, both closed and open-ended, as well as a Likert scale, structured around the following topics: definition, causes and forms of domestic violence, role and response of the health system to such cases, and services available for victims of domestic violence.

Only 21.5% of respondents knew that domestic violence is a crime and a violation of human rights due to the imbalance of power. This fact highlights the limited knowledge of the respondents and the presence of misconceptions about domestic violence. The study also reveals that the most recognized form of domestic violence is physical (in 95% of responses), followed by psychological (39.1%) and sexual violence (25.3%). It should be noted that 63.9% of respondents demonstrated the ability to recognize vulnerable categories of people subject to domestic violence.

An important aspect of the study was to assess medical practitioners' understanding of the health system's role in addressing domestic violence. The study findings highlighted that a notable proportion of respondents (34.9%) believe that the role of the health system in combating domestic violence is insignificant. On the other hand, it is encouraging to find that 70.9% of respondents (with a mean score of 3.8) agreed that a physician's inability to recognize victims of domestic violence affects the quality of medical care provided, thus acknowledging the major role they play in identifying and appropriately handling such cases. Regretfully, more than half of the respondents (61.3%) believe that documentation of injuries is an exclusive task of the forensic doctor (Table 1). This misconception affects the provision of evidence for the judicial act.

Table 1. Respondents' opinions on the role of the health system in addressing domestic violence

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Mean score
The role of the health system in combating domestic violence is insignificant	82 (9.9%, 95% CI 7.9–12.0)	208 (25.0%, 95% CI 22.0–28.0)	116 (13.9%, 95% CI 11.7-16.1)	171 (20.6%, 95% CI 17.9–26.6)	255 (30.6%, 95% CI 27.6–34.0)	2.7
Physicians' inability to identify victims of domestic violence affects the quality of medical care provided to them	285 (34.3%, 95% CI 31.1–37.7)	306 (36.8%, 95% CI 33.2–40.1)	97 (11.7%, 95% CI 9.4–13.9)	75 (9.0%, 95% CI 7.1–11.2)	69 (8.3%, 95% CI 6.4–10.3)	3.8
Medical care for victims of domestic violence can be affected by the doctor's misconceptions in this regard	156 (18.8%, 95% CI 16.2–21.3)	281 (33.8%, 95% CI 30.5–37.0)	202 (24.3%, 95% CI 21.5–27.2)	95 (11.4%, 95% CI 9.4–13.6)	98 (11.8%, 95% CI 9.6–13.9)	3.3
Documentation of injuries is an exclusive task of the forensic doctor	300 (36.1%, 95% CI 32.9–39.5)	210 (25.2%, 95% CI 22.4–28.0)	122 (14.7%, 95% CI 12.3–17.2)	90 (10.8%, 95% CI 8.5–13.0)	110 (13.2%, 95% CI 10.8–15.6)	3.4

Note: *Respondents' opinions on the role of the health system in addressing domestic violence are presented. Each statement is rated on a Likert scale (strongly agree, agree, neutral, disagree, strongly disagree). The table shows the distribution of responses and includes the mean score for each statement.*

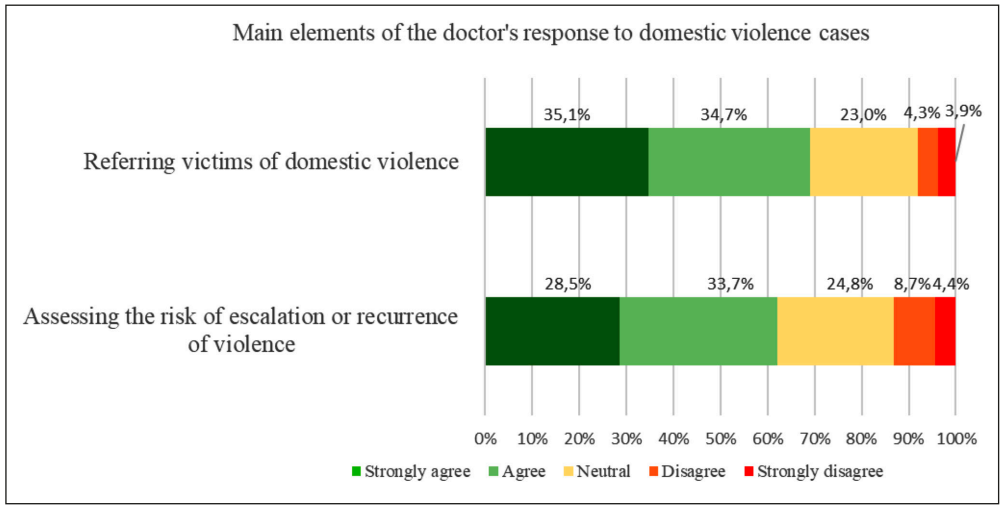

Fig. 1 Respondents' opinions on statements regarding their role in managing domestic violence cases

*The opinions of healthcare providers regarding two key aspects of managing domestic violence cases are presented. Each statement is rated by healthcare providers on a Likert scale (strongly agree, agree, neutral, disagree, strongly disagree). The figure likely illustrates the distribution of responses for both statements.

To assess healthcare providers' awareness of their role in addressing domestic violence, the authors asked respondents for their opinions on two important elements of the doctor's response to domestic violence cases. Responses revealed (Figure 1) that 69.8% of respondents agreed that referring victims of domestic violence is part of the doctor's response to domestic violence cases, as well as assessing the risk of violence escalation or recurrence (62.2%).

Additionally, the study investigated respondents' awareness of the barriers that prevent women survivors of domestic violence from accessing healthcare services and disclosing abuse to medical staff. Through an open-ended question, participants identified barriers such as *fear, shame, stigma, lack of information, distrust in the healthcare system, financial dependence on the abuser, and unawareness of their rights*. Furthermore, as an important barrier, 52.6% of respondents identified doctors' misconceptions in the field of domestic violence as a factor that could prevent victims from accessing quality healthcare services (Table 1). It is encouraging that doctors are aware of the real barriers

also described in the literature, as this would help them to anticipate and manage them appropriately, thus supporting victims to disclose cases of domestic violence in order to provide an effective and non-discriminatory response

The survey also included questions aimed at assessing respondents' knowledge regarding legal protection measures for victims of domestic violence. As a result, 89.1% of the participants did not know the legal protection measures. Thus, 88.5% of them wrongly consider that informing the social worker and/or the local mayor is an instrument of legal protection, and 11.5% believe that in the Republic of Moldova, there are no legal instruments for the protection of domestic violence victims. In terms of reporting to the police, only 33.8% of respondents knew that physicians have the duty to inform the police without the children's consent, and the adult victim's consent when a danger to her life and health is present. It's notable that 81.5% of respondents know that in the Republic of Moldova, there are support services for victims of domestic violence.

III. Assessment of respondents' perceptions and attitudes towards domestic violence

The third section was designed to assess respondents' perceptions and attitudes towards domestic violence and to identify misconceptions regarding this topic. It includes 16 closed-ended questions addressing how participants perceive the phenomenon of domestic violence, including opinions and personal experiences. The majority of the questions are Likert-scaled statements. Due to space constraints, this paper presents the analysis of only 6 questions. Table 2 illustrates five of the most widely believed and deep-rooted misconceptions in society and the respondents' opinions.

Table 2. Respondents' opinions on statements regarding their perceptions and attitudes toward DV

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Mean score
Domestic violence is a public health problem	512 (61.5%, 95% CI 58.4–65.1)	164 (19.7%, 95% CI 17.1–22.2)	92 (11.1%, 95% CI 8.9–13.2)	36 (4.3%, 95% CI 3.0–5.8)	28 (3.4%, 95% CI 2.2–4.8)	3.8
Domestic violence is a private issue	23 (2.8%, 95% CI 1.8–4.0)	58 (7.0%, 95% CI 5.4–8.7)	122 (14.7%, 95% CI 12.4–17.1)	133 (16.0%, 95% CI 13.5–18.4)	496 (59.6%, 95% CI 56.5–63.0)	2.3
Domestic violence occurs only in poor families	27 (3.2%, 95% CI 2.0–4.6)	160 (19.2%, 95% CI 16.7–21.9)	115 (13.8%, 95% CI 11.4–16.1)	182 (21,.9%, 95% CI 19.1–24.8)	348 (41.8%, 95% CI 38.7–45.1)	2.7
There are times when a woman deserves to be hit by her life partner	20 (2.4%, 95% CI 1.4–3.4)	25 (3.0%, 95% CI 1.9–4.2)	50 (6.0%, 95% CI 4.4–7.6)	52 (6.3%, 95% CI 4.7–8.1)	685 (82.3%, 95% CI 79.7–84.9)	2.1
Alcohol consumption is the cause of domestic violence	501 (60.2%, 95% CI 57.0–63.7)	209 (25.1%, 95% CI 22.0–28.0)	43 (5.2%, 95% CI 3.7–6.9)	33 (4.0%, 95% CI 2.8–5.5)	46 (5.5%, 95% CI 4.0–7.2)	3.9

Note: *Respondents' opinions on various statements regarding their perceptions and attitudes toward domestic violence are presented. Each statement is rated on a Likert scale (strongly agree, agree, neutral, disagree, strongly disagree). The table displays the distribution of responses. Additionally, the table includes the mean score for each statement, providing a summary measure of the overall trend in respondents' attitudes and perceptions.*

The results revealed that 81.2% of participants consider domestic violence a public health problem, and 85.6% of them vehemently disagree that domestic violence is a private issue. Moreover, 91.9% of the participants demonstrated their position against this phenomenon by firmly stating that domestic violence is unacceptable under any circumstances. A higher proportion of the participants (88.6%) strongly disapprove of the idea that women sometimes deserve to be hit by their life partner.

However, 22.4% of respondents believe that domestic violence occurs only in poor families, and almost all the participants (85.3%) think that alcohol consumption is the cause of domestic violence.

Participants also strongly disagree (88.6%) that sometimes a woman deserves to be hit by her life partner, which demonstrates again that they are familiar with the physical form of domestic violence.

The authors note that there were no statistically significant differences in the responses to all the aforementioned statements and questions based on the respondents' essential characteristics, including gender, age, marital status, and work status.

Discussion

The essential point in selecting the sample was that domestic violence is a public health problem, and it is crucial for doctors to have specific knowledge and skills to ensure an adequate response and prevention of the phenomenon. The authors noted that 85.7% of the respondents in this survey shared the same opinion. Moreover, 88.7% of them confirmed this by stating that the main reason for attending future training in this field is that they are aware of the problem and want to be informed.

The present study highlights the need for improvement in respondents' knowledge and attitudes towards violence. The answers to the second part of the questionnaire, which targeted elementary knowledge about the general concept and role of the health system in addressing cases of domestic violence, showed that respondents are not fully aware of what the concept of domestic violence is and what forms it can take. This knowledge is fundamental for providing effective support and assistance to victims of domestic violence and can significantly affect the health and well-being of DV victims.

This observation is also demonstrated by the fact that even the participants recognized themselves as possessing an insufficient level of knowledge, with more than half rating it as medium or lower. We strongly believe that this can be explained by the fact that 60.8% of respondents had not previously received training in this area, which likely influenced their self-assessment of knowledge. It is remarkable that 70.0% of respondents are aware of their own deficiencies in understanding how they should react in such cases and are interested in attending training in this field. 88.7% of them said that one of the reasons they would attend training again is that they are aware of the problem and want to be informed.

Only 21.5% of participants were aware of the definition of domestic violence, but only a limited number (around 1%) of them were able to state all forms of domestic violence. The most recognized was physical violence, despite Law No. 45/2007 *on preventing and combating domestic violence* stipulating five forms of domestic violence: physical, sexual, psychological, spiritual, and economic [4]. In our study, we found that the least recognized forms of domestic violence were spiritual and economic ones. We consider that limited awareness of healthcare providers about all forms of domestic violence can lead to overlooked cases and inadequate responses, as well as restricting the victims' access to high-quality and need-tailored healthcare services.

It is important to underline that 34.9% of the participants think the role of the health system in combating domestic violence is insignificant. This observation leads us to believe that they are not fully aware of the contribution they have made in addressing this important problem. The existence of such an opinion among more than a third of medical professionals is quite worrying, as it contradicts the general conception of the importance of the medical system in dealing with domestic violence. Thus, underestimating this role could lead to inadequate provision of assistance to victims of domestic violence and undermine efforts to prevent this serious phenomenon. However, more than half of respondents recognized referring DV victims and assessing the violence escalation risk as elements of the physicians' response to domestic violence. This suggests that participants are still aware that they are playing a significant role in addressing this issue, but not in a good enough manner.

To ensure the victim's safety and protection, health workers must inform the victim about existing legal protection measures. Unfortunately, our study revealed that current and future physicians do not know them, which can affect the victims' ability to ask for these measures. According to Moldovan legislation [4, 21], healthcare providers must report DV cases to the police when children are involved and a danger to an adult victim's life or health is present without their consent. Regrettably, only a third of respondents knew about this duty. This gap can lead to a late start of a criminal case and increase risks of violence recurrence.

Healthcare providers, like many other members of society, can be affected by misconceptions and stereotypes about domestic violence and women subjected to violence. Misconceptions and stereotypes associated with domestic violence may influence how health professionals understand and respond to cases of domestic violence in their professional practice. For appropriate and effective intervention, healthcare professionals must distinguish between myths and the reality that underlies the phenomenon of domestic violence. To assess respondents' perceptions and attitudes towards the phenomenon of domestic violence, the authors used a series of well-known myths to find out the participants' opinions. Myths are ideas and beliefs that have no objective foundation and are not based on facts. These misconceptions disseminate incorrect information about the phenomenon and its origins, influencing how it is perceived and how society reacts to cases of violence [20].

The study revealed that domestic violence is seen by doctors as a public health problem and not as a private issue. Despite respondents' belief that there are no circumstances which would excuse the application of force against a woman, they are still affected by some myths. Thus, they wrongly think that DV occurs only in poor families and alcohol consumption is its cause. It is well known that myths are harmful, as they distort the actual situation of domestic and gender-based violence, and due to this fact, they can discourage healthcare professionals' intervention [20].

Conclusions

The study revealed that current and future doctors strongly need to be trained in order to strengthen their capacity to adequately respond to cases of domestic violence. Analysis of perceptions showed that medical respondents are still affected by some stereotypes, as other members of society, but to a lesser extent. The National Strategy on preventing and combating domestic violence stipulates the compulsory nature of both primary and continuous education for medical staff in the field of domestic violence. The results of this study provide an overview of current and future physicians' knowledge and approaches and may be used as evidence-based proposals for enriching existing training programs or designing new ones, in order to support healthcare practitioners in the proper management of domestic violence cases. Proper knowledge and attitudes are essential to ensure respect for human rights and the effective implementation of the Council of Europe Convention on Preventing and Combating Violence against Women and Domestic Violence (2011) in the Republic of Moldova.

Competing interests

None declared.

Authors' contributions

AP conceived the study, contributed to its design, and assisted in drafting the manuscript. PG and AB designed the questionnaire, collected the data, and conducted its analysis. All authors critically reviewed the manuscript and approved the final version.

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Ethics approval

The study was approved by the Research Ethics Committee of *Nicolae Testemiţanu* State University of Medicine and Pharmacy (Minutes 3 from May 18, 2023).

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RESEARCH ARTICLE

Interdental contact – morphofunctional component of the stomatognathic system

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ABSTRACT

Introduction. As part of the interproximal assembly, the interdental contact is a morphofunctional component that contributes to the stabilization of teeth, maintaining the integrity of the dental arch, protecting the papilla, and preventing food impaction. The aim of the study is to radiologically evaluate the proximal morphology of restored surfaces on lateral teeth and the positioning of the interdental contact.

Material and methods. The study was performed by analyzing 100 digital bite-wing radiographs that showed proximal restorations on lateral teeth, which were related to a neighboring tooth in order to mark an interproximal area. The data obtained were analyzed statistically.

Results. The restored surfaces exhibited a convex emergence profile in 71% of cases, a straight one in 26%, and a concave in 3%. A harmonious cervical marginal adaptation was observed in 66% of proximal restorations, while 33% showed defective cervical marginal adaptation. In 81% of cases, interdental contact was identified, while in 19% of cases, it was absent. Out of the 81 cases that exhibited interdental contact, 34.6% had an anatomical positioning, and 65.4% non-anatomical one.

Conclusions. The radiological assessment of proximal restorations on lateral teeth and of interdental contacts found that they do not always meet anatomical requirements and fail to fulfill all qualitative parameters. Concave and straight emergence profiles of restorations, the presence of invaginations and overhangs at the cervical level, absence of interdental contact, or its non-anatomical positioning indicate the necessity to revise the principles of restoring proximal surfaces on lateral teeth by using accessories to restore the interproximal relationship according to the clinical situation.

Keywords: interdental contact, emergence profile, bite-wing radiography.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

While significant research has been conducted on the anatomy and function of interdental contacts, there is still limited data on the radiological evaluation of the proximal morphology of restored surfaces in lateral teeth. The emergence profile and marginal adaptation of restorations, as well as the presence of interdental contact and its positioning are the studied aspects, which have a great importance in following the biomimetic concept.

The research hypothesis

Restorations of proximal surfaces in lateral teeth exhibit significant variations in contact area size, emergence profile, location, and tightness when evaluated radiologically, compared to natural interdental contacts. The restorations following biomimetic

principles will demonstrate superior interdental contact integrity, minimizing the risk of food impaction, periodontal issues, and secondary caries.

The novelty added by manuscript to the already published scientific literature

The novelty of this manuscript lies in its radiological evaluation of the proximal morphology of restored surfaces on lateral teeth, specifically analyzing the accuracy of interdental contact positioning. While previous studies have described the anatomical and functional significance of interdental contacts, limited research has focused on their restoration outcomes in clinical practice. This study contributes new insights into the impact of restorative techniques on interdental contact integrity, highlighting the importance of biomimetic principles in achieving optimal anatomical and functional rehabilitation.

Introduction

In contemporary medical practice, the most crucial criterion for treatment success is the restoration of the anatomical form and functional value of the affected organ or system [1, 2]. A significant challenge for dental practitioners is the restoration of proximal surfaces on lateral teeth, as the operative treatment of carious lesions focuses on reestablishing the anatomical and physiological characteristics of interproximal relationships.

The interproximal relationship is defined as the correlation between neighboring teeth of the same dental arch or the relationship that exists between the mesial surface of one tooth and the distal surface of the adjacent tooth. As a fundamental element of the interproximal assembly, the restoration of the interdental contact results from understanding its functionality. It is defined as the location where the maximum prominence area of the mesial or distal contour of a tooth contacts its adjacent counterpart in the same arch [3, 4]. Studies have found that the interproximal contact established by intact natural teeth takes the form of a point in individuals up to 20 years old; in individuals aged 20-40 years it is represented by a surface area of 1.5 mm^2; and in individuals over 40 years old, it reaches a surface area of 4.5 mm^2 [5]. This is due to physiological dental movements during the masticatory process that generate friction between neighboring teeth at their contact point, transforming the point into a more or less extended surface, which is determined by the direction and axis of movements. In the case of lateral teeth, the predominant axis is transversal, resulting in movements towards the free surfaces. Physiological mobility is higher in erupting teeth, in women compared to men, in children compared to adults, and is lower in teeth without antagonists or those with severe attrition. Measurements taken in individuals aged 45-50 years with a healthy oral cavity and complete dentition have shown 10 mm of enamel abrasion from the contact areas of teeth in one arch. This is approximately 0.38 mm per contact area of each tooth [4, 6]. Thus, in older individuals, the contact area has a larger and flatter surface [7].

Anatomically, the contact surface is located at the level of the maximum contour of the proximal surfaces. For lateral teeth, it is positioned at the transition between the middle and occlusal third of the cervico-occlusal distance and at the transition between the middle and buccal third of the buccal-oral distance [8]. Some studies have found that the size, location, and shape of contact areas also depend on the anatomical contours and convergence of proximal surfaces, respectively, the mesial or distal placement [9].

The importance of properly restoring the interdental contact is determined by the series of its functions:

- stabilizes the position of the teeth, facilitating the transmission of masticatory forces;
- maintains the integrity of the dental arch;
- prevents food impaction, which in turn can cause masticatory discomfort, recurrent dental caries, periodontal disease, or lead to dental migration;
- protects the interdental papilla by diverting food towards the buccal and oral direction, preventing trauma and inflammation [4, 7, 10].

Alongside anatomical positioning, an essential criterion is the tightness of interdental contact. A sufficiently tight proximal contact resists separation forces during mastication and prevents food impaction. Lack of contact or insufficient tightness is associated with periodontal disease, tooth tilting, disturbance of occlusal relationships with antagonists, and retention of bacterial plaque in the interproximal space [11].

Thus, the cornerstone in interdental contact management is adhering to the biomimetic concept, which involves restoring of the damaged portions of the tooth according to the natural tooth's characteristics regarding appearance, biomechanical competencies, and function [12].

The purpose of the study was to radiologically evaluate the proximal morphology of restored surfaces on lateral teeth and the positioning of interdental contact.

Material and methods

The study included 100 digital bite-wing radiographs, which according to the literature, are the most effective for the diagnosis of proximal lesions on lateral teeth, the assessment of qualitative parameters of proximal restorations, as well as the positioning of the contact area. Bite-wing radiographs were selected based on the presence of proximal restorations on lateral teeth which were related to a neighboring tooth, marking an interproximal area. They included the I premolar – II molar area and were taken over the course of one year.

The restorations were analyzed according to their location:

- at the level of molars or premolars;
- in the upper or lower arch;
- on the mesial or distal surface.

The proximal morphology of the restorations was evaluated by assessing the emergence profile categorized as concave, convex, or straight surface. Similarly, the cervical marginal adaptation of the restoration was studied by evaluating the presence of a harmonious transition between tooth and restoration or a visible radiographic overhang (Fig. 1), with the calculation of its size.

The adjacent tooth to the restoration was assessed as:

- intact tooth without proximal cavity lesion (Fig. 2);
- tooth with proximal restoration (the emergence profile of the restoration was determined) (Fig. 3);
- tooth with crown coverage (the emergence profile of the crown was determined).

Subsequently, the interdental contact was analyzed by evaluating its presence or absence (Fig. 4), as well as its positioning in the cervico-occlusal direction, with the establishment of anatomical or non-anatomical localization.

For lateral teeth, where the contact area is anatomically positioned at the maximum contour of the proximal surfaces and at the transition between the middle and occlusal third of the cervico-occlusal distance, three distances were calculated (Fig. 5):

- distance between adjacent teeth at the cemento-enamel junction (CEJ);
- distance from the CEJ to the middle of the contact area;
- distance from the CEJ to the occlusal edge, along the cervico-occlusal distance.

To calculate the middle of the cervico-occlusal distance, the following formula was applied:

$$Middle\ of\ the\ cervico-occlusal\ distance = \frac{Distance\ from\ the\ CEJ\ to\ the\ occlusal\ edge}{2}$$

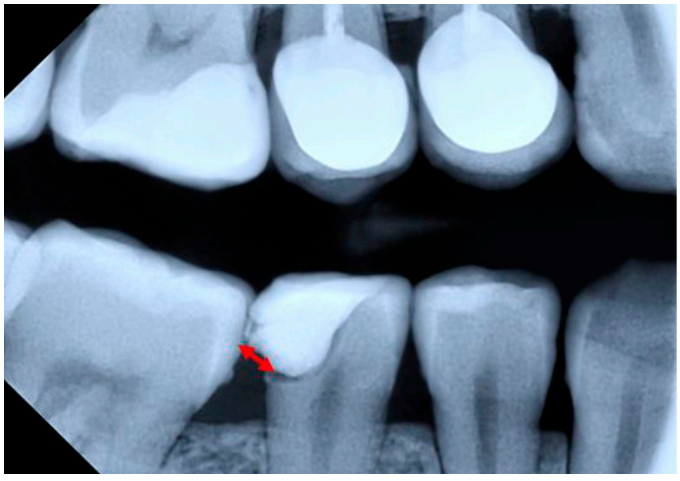

Fig. 1 Bitewing radiography. Distal restoration in tooth 45 with the presence of overhang.

***Note**: Red line – overhang.*

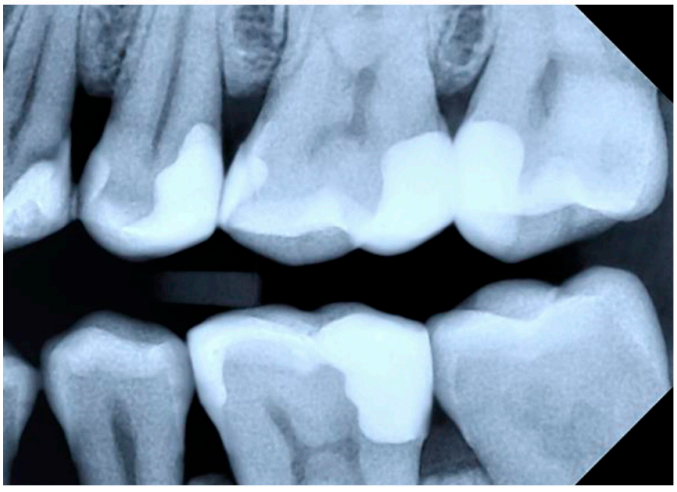

Fig. 3. Bitewing radiography.

Distal restorations in teeth 24, 25, 26 with adjacent teeth with proximal restorations.

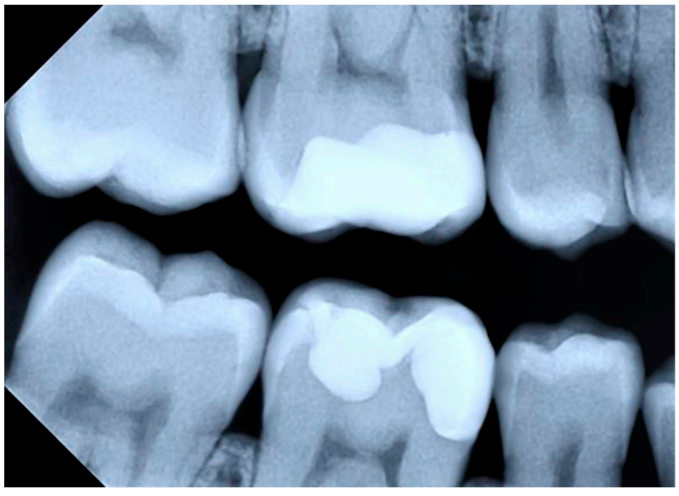

Fig. 2. Bitewing radiography.

Mesial restoration (convex emergence profile) in tooth 16 with intact adjacent tooth. Mesial restoration (convex emergence profile) in tooth 46 with intact adjacent tooth.

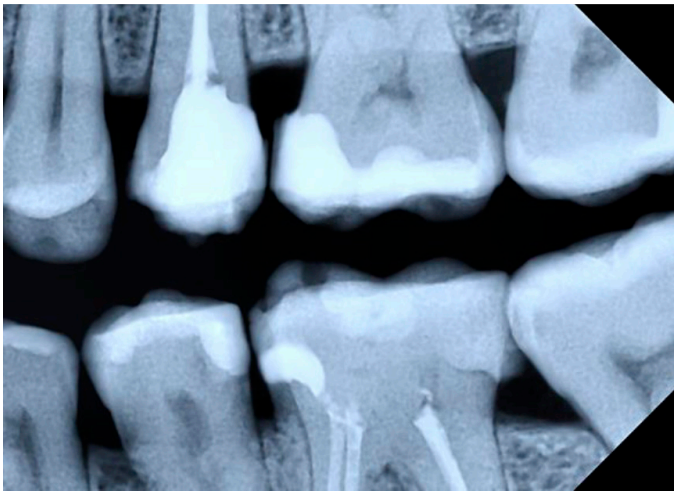

Fig. 4. Bitewing radiography.

Proximal restorations with the absence of interdental contact between teeth 25-26, 35-36.

To calculate the occlusal third of the cervico-occlusal distance, the following formula was applied:

$$occlusal\ third\ of\ the\ cervicoocclusal\ distance = \frac{distance\ from\ the\ CEJ\ to\ the\ occlusal\ edge}{3}$$

Thus, the anatomical positioning of the interdental contact was considered to fall within the interval between the point representing the middle of the cervico-occlusal distance and the point representing 2/3 of the cervico-occlusal distance, calculated from the cervical level.

The obtained data were subjected to statistical evaluation with the software Epi Info 7.2 and Microsoft Excel 2019 in order to establish statistical differences in the sample studied. For this, a95% confidence interval was calculated. A significant level (p-value) of 0.05 was set to indicate whether the observed differences were statistically significant.

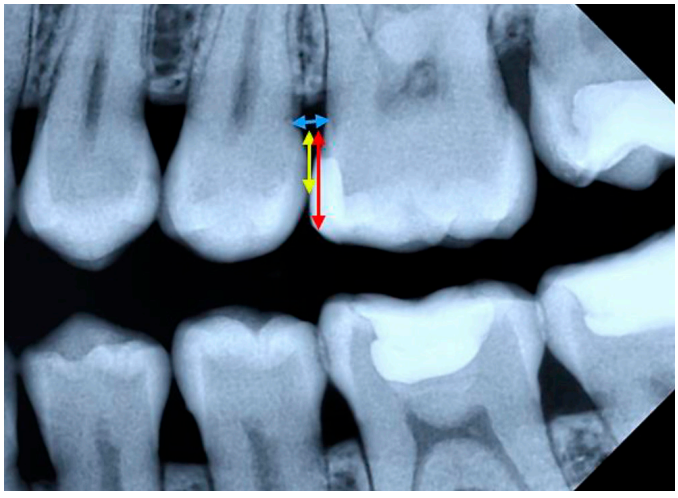

Fig.5 Bitewing radiography. Distances measurements.

Note: *Blue line - distance between adjacent teeth at the cemento-enamel junction (CEJ). Yellow line - distance from the CEJ to the middle of the contact area. Red line - distance from the CEJ to the occlusal edge, along the cervico-occlusal distance.*

Results

By analyzing the proximal restorations' location based on the obtained data from 100 bite-wing radiographies, the following results were obtained.

Analysis of proximal restorations regarding their location. Table 1 shows the data at the level of molars or premolars.

Table 1. Location of restoration according to tooth type.

Molar or premolar	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
Molar	42	42,0 %	32,2 %	52,3 %
Premolar	58	58,0 %	47,7 %	67,8 %
TOTAL	100	100,00 %		

Note: *Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

The table provides data on the distribution of restorations at the level of molars and premolars in a sample, where restorations at the molar level represent 42.0% (95% CI: 32.2-52.3) of the total 100 observations, while restorations at the premolar level are present in 58.0% (95% CI: 47.7-67.8) of cases.

By comparing the confidence intervals, it can be assessed if there is a statistically significant difference between the proportions of restorations at the molar and premolar levels. In this case, the two 95% confidence intervals overlap, indicating that there is no significant difference between the frequency of restorations at the molar and premolar levels in the sample studied (p>0.05). Table 2 demonstrates the data at the level of the upper or lower arch.

Table 2. Location of restoration according to the dental arch.

Upper or lower dental arch	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
Upper dental arch	61	61,0 %	50,7 %	70,6 %
Lower dental arch	39	39,0 %	29,4 %	49,3 %
TOTAL	100	100,00 %		

Note: *Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

The table provides data on the distribution of restorations in the upper or lower arch in a sample, where restorations in the upper arch represent 61.0% (95% CI: 50.7-70.6) of the total 100 observations, while restorations in the lower arch are present in 39.0% (95% CI: 29.4-49.3) of the cases. In this case, the two intervals do not overlap, indicating a difference ($p < 0.05$) between the frequency of restorations in the upper and lower arches in the studied sample. Table 3 represents the data at the level of mesial or distal surface.

Table 3. Location of restoration according to the proximal surface of the tooth

Mesial or distal surface	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
Mesial surface	40	40,0 %	30,3 %	50,3 %
Distal surface	60	60,0 %	49,7 %	69,7 %
TOTAL	100	100,00 %		

Note: *Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant*

The table presents the distribution of restorations based on the location on the mesial or distal surface of the tooth in a sample studied. Restorations on the mesial surface of the tooth constitute 40.0% (95% CI: 30.3-50.3) of the total 100 observations, while restorations on the distal surface represent 60.0% (95% CI: 49.7-69.7). In this context, the fact that the two intervals almost do not overlap suggests an insignificant difference in the frequency of restoration localization on the mesial or distal surfaces in the studied sample.

Table 4. Emergence profile of the restored surface.

Convex, concave or straight	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
Convex	71	71,0 %	61,1 %	79,6 %
Concave	3	3,0 %	0,6 %	8,5 %
Straight	26	26,0 %	17,7 %	35,7 %
TOTAL	100	100,00 %		

Note: *Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

Table 4 provides the distribution of convex, concave, and straight emergence profiles of the restored surface in a studied sample. Out of a total of 100 observations, the convex emergence profile is the most common, representing 71.0% (95% CI: 61.1-79.6), followed by the straight emergence profile at 26.0% (95% CI: 17.7-35.7), and the concave emergence profile at 3.0% (95% CI: 0.6-8.5). In this case, the three confidence intervals do not completely overlap, indicating a possible significant difference in the frequency of these profiles in the studied sample ($p < 0.05$).

This suggests that the convex emergence profile of the restored surface is the most commonly encountered, while the concave emergence profile is the least encountered. However, to confirm these observations and assess the statistical significance of the observed differences, it is advisable to use additional statistical methods such as hypothesis testing or regression analysis.

Table 5. Cervical marginal adaptation of the proximal restoration.

Adapted, overhang, invagination	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
A	66	66,0 %	55,8 %	75,2 %
I (0,4)	1	1,0 %	0,0 %	5,4 %
O (0,1)	3	3,0 %	0,6 %	8,5 %
O (0,2)	4	4,0 %	1,1 %	9,9 %
O (0,3)	6	6,0 %	2,2 %	12,6 %
O (0,4)	5	5,0 %	1,6 %	11,3 %
O (0,5)	5	5,0 %	1,6 %	11,3 %
O (0,6)	4	4,0 %	1,1 %	9,9 %
O (0,7)	1	1,0 %	0,0 %	5,4 %
O (0,8)	1	1,0 %	0,0 %	5,4 %
O (0,9)	3	3,0 %	0,6 %	8,5 %
O (1,1)	1	1,0 %	0,0 %	5,4 %
TOTAL	100	100,00 %		

Note: *A - adapted, O - overhang, I – invagination; Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

Table 5 provides the distribution of cervical marginal adaptations of proximal restorations in a studied sample, where "A" represents harmonious adaptation, "O" represents the presence of an overhang, and "I" represents the presence of an invagination at the cervical level.

Out of a total of 100 observations, harmonious adaptation "A" is the most commonly encountered, representing 66.0% (95% CI: 55.8-75.2). The presence of invagination "I" and the presence of an overhang "O" are less frequent, representing 1.0% (95% CI: 0.0-5.4) and 3.0% (95% CI: 0.6-8.5) respectively.

The difference between the observed frequencies suggests that harmonious cervical marginal adaptation of the restoration is predominant ($p < 0.05$) compared to the other two types of adaptation. However, 34% of cases show a non-harmonious cervical marginal adaptation, represented by an overhang or invagination.

Table 6. Adjacent tooth to the restored proximal surface.

Intact, restoration, crown	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
In	35	35,0 %	25,7 %	45,2 %
R	61	61,0 %	50,7 %	70,6 %
Co	4	4,0 %	1,1 %	9,9 %
TOTAL	100	100,00 %		

Note: *In - intact, R - restoration, Co - crown; Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

Table 6 provides the distribution of the adjacent tooth's condition to the restored proximal surface, which can be intact "In", restored "R", or having a crown "Co", in a studied sample.

Out of a total of 100 observations, it is underlined that the majority of adjacent teeth are restored, representing 61.0% (95% CI: 50.7-70.6). The intact adjacent tooth constitutes 35.0% (95% CI: 25.7-45.2), while the presence of a crown is observed in 4.0% (95% CI: 1.1-9.9) of cases. This distribution suggests that the restored adjacent tooth is the most commonly encountered ($p < 0.05$) among the adjacent teeth, followed by the intact adjacent tooth and the one with a crown.

Table 7. Emergence profile of the adjacent tooth surface (convex, concave, straight).

Adjacent tooth surface convex, concave, straight	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
Convex	84	84,0 %	75,3 %	90,6 %
Straight	16	16,0 %	9,4 %	24,7 %
TOTAL	100	100,00 %		

Note: *Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

Table 7 provides data on the distribution of the emergence profile of the adjacent tooth surface in a specific sample, classifying the surfaces as convex, concave, or straight. Out of a total of 100 observations, it can be noted that the surfaces of the adjacent tooth are predominantly convex, representing 84.0% (95% CI: 75.3-90.6) of the total. In contrast, straight surfaces are recorded in a smaller proportion, accounting for only 16.0% (95% CI: 9.4-24.7), while concave surfaces are absent.

These findings indicate that convex surfaces are the most common ($p < 0.05$) among the adjacent teeth, suggesting a predominant trend towards this shape. At the same time, straight surfaces are less common in this sample.

Table 8. Interdental contact (presence, absence).

Presence, absence of interdental contact	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
Presence	81	81,0 %	71,9 %	88,2 %
Absence	19	19,0 %	11,8 %	28,1 %
TOTAL	100	100,00 %		

Note: *Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

Table 8 presents the distribution of interdental contact in a studied sample, categorizing the contact as either "present" or "absent". Out of a total of 100 observations, it is observed that the majority of interproximal relationships have interdental contacts, representing 81.0% (95% CI: 71.9-88.2). In contrast, the absence of interdental contact is observed in 19.0% (95% CI: 11.8-28.1) of cases.

These findings suggest that in the majority of cases, there is interdental contact ($p < 0.05$). However, it is important to note that approximately one-fifth of cases exhibit the absence of the contact.

Table 9. Distance between adjacent teeth at the CEJ.

Distance, mm	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
0,5-1	3	3,0 %	0,6 %	8,5 %
1,1-1,5	18	18,0 %	11,0 %	26,9 %
1,6-2,0	42	42,0 %	32,2 %	52,3 %
2,1-2,5	31	31,0 %	22,1 %	41,0 %
2,6-3,0	3	3,0 %	0,6 %	8,5 %
> 3	3	3,0 %	0,6 %	8,5 %
TOTAL	100	100,00 %		

Note: *CEJ – cemento-enamel junction; Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

Table 9 provides information on the distribution of the distance between adjacent teeth at the cemento-enamel junction (CEJ). The distance is divided into intervals to allow for a more detailed analysis of the distribution of these measurements.

Out of the 100 recorded observations, it can be emphasized that the intervals 1.6-2.0 and 2.1-2.5 dominate the distribution, representing 42.0% (95% CI: 32.2-52.3) and 31.0% (95% CI: 22.1-41.0) of the total sample, respectively. This suggests that the majority of distances between adjacent teeth at the CEJ fall within these intervals.

Additionally, it can be noticed that smaller intervals, such as 0.5-1 and 1.1-1.5, represent lower percentages of the total sample, indicating that smaller distances are less common in this study. The intervals represent 3.0% (95% CI: 0.6-8.5) and 18.0% (95% CI: 11.0-26.9) of the sample, respectively.

Regarding larger values, from 2.6-3.0 and above 3, these are less frequently encountered, each representing 3.0% (95% CI: 0.6-8.5) of the sample. This may suggest the presence of some exceptional cases where the distance between teeth is greater.

Table 10. Mean and median of the distance between adjacent teeth at the CEJ.

	Obs	Mean	Std Dev	Min	Median	Max
Distance between adjacent teeth at the level of CEJ	100	1,8	0,5	0,8	1,8	4,4

Note: *CEJ – cemento-enamel junction; Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

These data provide insight into the distribution of the distance between adjacent teeth at the CEJ within the sample studied. The mean distance between adjacent teeth at the CEJ is approximately 1.8 mm, with a standard deviation of 0.5, indicating that the majority of observations clusters are around mean value, with moderate dispersion. There is significant variation in the distance between adjacent teeth within the sample, with a minimum recorded value of 0.8 and a maximum value of 4.4. This variation demonstrates significant differences in tooth spacing among the analyzed cases.

The median distance between teeth at the CEJ is 1.8, indicating that half of the observations have a distance less than or equal to 1.8, while the other half have a distance greater than or equal to 1.8. This highlights a relatively balanced distribution of data around the median.

Table 11. Positioning of the interdental contact (anatomical, non-anatomical).

Anatomical, non-anatomical	Abs.	Percent	Exact 95% LCL	Exact 95% UCL
Anatomical	28	34,6 %	24,3 %	46,0 %
Non-anatomical	53	65,4 %	54,0 %	75,7 %
TOTAL	81	100,00 %		

Note: *Abs – absolute value; LCL – Lower Confidence Limit; UCL – Upper Confidence Limit. Statistical evaluation was performed with the software Epi Info 7.2. Descriptive analysis was provided. Confidence Interval (CI) – 95% was calculated. A significant level (p-value) of 0.05 was considered statistically significant.*

The table presents the distribution of the positioning of the interdental contact within the studied sample, classified into anatomical and non-anatomical. In this category, anatomical positioning accounts for 35.0% (95% CI: 24.7-46.5) out of a total of 81 observations, indicating that approximately one-third of dental contacts are considered anatomically positioned. The distribution ($p < 0.05$) is dominated by non-anatomical positioning which represents 65.0% (95% CI: 53.5-75.3) of the total sample. This suggests that the majority of dental contacts are positioned in a manner considered non-anatomical.

Discussion

Reproducing an anatomical proximal contour represents a primary objective in proximal restorations and is crucial for maintaining the health of the underlying periodontal tissues [13]. Similarly, it minimizes the risk of recurrent caries as a complex multifactorial process that requires careful analysis of the restoration, along with the chemical and bacterial effects of the oral environment [14].

The results of the study showed that restorations at the level of lateral teeth are more commonly encountered in the upper dental arch than in the lower one and on distal surfaces more than mesial ones. The increased frequency of carious lesions in the upper teeth underlines the necessity for restorative treatment. This finding may be influenced by the reduced visibility of teeth in the upper arch by the patient, leading to late detection of carious processes and delayed referral to the dentist for treatment. The prevalence on distal surfaces is determined by poorer oral hygiene in this region, with difficulties in using adjunctive oral hygiene aids such as floss and interdental brushes. This increases the risk of bacterial plaque accumulation, which is the determining factor in the onset of carious process.

Regarding the evaluation of the emergence profile of the restored surfaces, a predominance of the convex profile, considered anatomical, was observed. However, a fairly high percentage of straight and concave profiles, classified as non-anatomical, were also evident. This leads to the difficulty of achieving an anatomical interdental contact, which according to the definition is formed by the maximum proximal prominence areas of the adjacent teeth.

The cervical marginal adaptation of restorations may present either a harmonious transition between the tooth and the restoration or the presence of an invagination and cervical overhang. These irregularities represent plaque retention areas, making oral hygiene challenging and potentially leading to restoration displacement, jeopardizing the success of restorative treatment and its maintenance over time. Mjor *et al.* reported that the gingival wall of the proximal restoration on lateral teeth is the most common site of recurrent caries [15-17].

The data obtained in the current study are consistent with those reported in a previous cross-sectional study, which highlighted that one-third of the analyzed proximal restorations had secondary marginal overhangs [18]. The occurrence of such areas of unsatisfactory marginal adaptation is conditioned by factors centered on the dentist, revealing gaps in following the principles of proximal surface restoration in lateral teeth, including the inappropriate use of matrices, interdental wedges, and separation rings depending on the present clinical situation.

As a result of obtaining a deficient emergence profile and unsatisfactory marginal adaptation, cases of missing interdental contact were noted. However, its presence prevails in the conducted study, indicating that even in the case of a deficient emergence profile, an interdental contact can be achieved. Nevertheless, it is essential to evaluate the contact's tightness, which is much more important than its mere presence. Studies have concluded that the presence and tightness of the interdental contact are determined by the type of restored tooth, its location, the time of day when it was restored, the periodontal status of the tooth, and manifest a high degree of individual variability [8].

Similarly, the positioning of the contact area plays an essential role in performing its functions. The respective study found that in the majority of cases, the interdental contact was present, but it corresponded to a non-anatomical positioning, which prevailed over the anatomical one. This finding may also be influenced by the distance between adjacent teeth at the CEJ, so that a greater distance requires the use of special anatomical sectional matrices with larger curvatures, which are not possessed by every practitioner. Thus, the distance influences the presence of the interdental contact and its anatomical positioning.

Conclusions

The radiological assessment of proximal restorations on lateral teeth and of interdental contacts found that they do not always meet anatomical requirements and fail to fulfill all qualitative parameters. Concave and straight emergence profiles of restorations, the presence of invaginations and overhangs at the cervical level, absence of interdental contact, or its non-anatomical positioning indicate the necessity to revise the principles of restoring proximal surfaces on lateral teeth, by using accessories to restore the interproximal relationship according to the clinical situation.

Competing interest

None declared.

Authors' contributions

VA performed the study, drafted the first manuscript and interpreted the data; DM completed the final text, and SC revised the manuscript. All the authors approved the final version of the manuscript.

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The study was the authors' initiative. The authors are independent and take responsibility for the integrity of the data and accuracy of the data analysis.

Patient consent

Obtained.

Ethics approval

The study was done within the doctoral program whose research project was approved by the Committee of Research Ethics with number 1 on 12.11.2021.

Provenance and peer review

Not commissioned, externally peer review.

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RESEARCH ARTICLE

Principles of effective communication with elderly patients in community pharmacy practice

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ABSTRACT

Introduction. Effective communication techniques within the pharmaceutical system enhance the pharmacist's image as a medication expert. Emphasizing these communication principles helps pharmacists create a favorable environment during counseling session with elderly patients, addressing their specific needs and expectations.

The aim of the study was to highlight the principles and general rules of communication adapted to the needs of elderly individuals as beneficiaries of specialized pharmaceutical care and to ensure the quality of pharmaceutical services provided to them in community pharmacies.

Materials and methods. The research conducted was descriptive in nature, and the research instrument used was a questionnaire consisting of eight closed-ended questions that focused on various aspects of information exchange between pharmacists and elderly patients during medication dispensing.

Results. A survey of 406 community pharmacists revealed that they are key sources of information in elderly patients' medication decisions. By asking questions about medications and health conditions, pharmacists engage patients and enhance interactions. Identifying and overcoming communication barriers in the pharmacist-elderly patient relationship depends on the techniques and tools used by pharmacists. Most respondents indicated that they rarely encounter communication barriers with elderly patients during counseling. Open and effective communication, along with adapting language to the patient's level of understanding, supports accurate medication counseling and helps prevent errors. Applying effective communication principles ensures that elderly patients receive necessary information about their medication, especially in the case of minor ailments. Elderly patients frequently seek advice on issues such as muscle pain, insomnia, constipation, and cough. In these cases, pharmacists recommend and select appropriate over-the-counter medications for them. Implementing a counseling algorithm for elderly patients in community pharmacies could significantly improve communication quality and patient outcome.

Conclusions. Standardized communication techniques, such as an elderly-centered counseling algorithm, can help prevent medication errors and promote rational medication use in outpatient settings, especially for minor ailments.

Keywords: effective communication principles, community pharmacy, pharmaceutical care, elderly patients.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

While the principles of effective communication with elderly patients are well known, pharmacists often face unique challenges in applying them to establish meaningful relationships. Overcoming these challenges requires pharmacists to prioritize patient-centered communication strategies.

The research hypothesis

Applying effective communication principles in pharmacies–prin-

ciples that consider the specific needs and limitations of elderly patients–can significantly improve their understanding of medication use, adherence to treatment, and overall satisfaction with pharmacy services.

The novelty added by the manuscript to the already published scientific literature

The research led to the development of a tailored counseling algorithm designed specifically for pharmacists. This algorithm is integrated into the specialized pharmaceutical care guide, providing up-to-date approaches for addressing the needs of high-risk patient categories, such as elderly people.

Introduction

The deontological code of the pharmacist states: "In his or her activity, the pharmacist must respect the honor and dignity of the patient, with the obligation to assist all patients visiting the community pharmacy equally and to correctly inform them about the requested medications" [1]. Effective communication between the patient and the pharmacist, as well as with other healthcare professionals, is important for enabling patients to make informed decisions regarding their medication and to ensuring the rational use of medications. This principle is regulated by the Good Pharmacy Practice Rules [2] and is part of the continuous evolution of the pharmacist's role in the healthcare system. Communication is an extremely complex field that involves not only the transmission of content but also interpersonal relationships and social processes. Researching the principles of communication in pharmaceutical practice allows for improving and ensuring the quality of pharmaceutical services provided in community pharmacies and other patient care settings [3]. Effective communication is one of the professional standards of the pharmacist, promoted by various international organizations in the field [4-8], which contribute to improving the health, safety, and well-being of patients. Interpersonal communication skills are considered so important that they are an essential component in educational programs/curricula developed by the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties [9].

According to the General Pharmaceutical Council, „Communication can take many forms and manifest in different ways. Effective communication is essential for providing person-centered care and collaborating with others. It helps people to be involved in decisions related to their health, safety, and well-being. Communication means more than just providing information, asking questions, and listening. It involves the exchange of information between people. Body language, tone of voice, and the words used by pharmaceutical professionals all contribute to effective communication" [8].

Effective communication in the community pharmacy requires each interaction to include a clear and concise message from the pharmacist, as well as a patient who can understand and interpret that message. The patient also provides feedback to the pharmacist in response to the received message [10].

Effective verbal communication is defined as the exchange of information using words understood by the receiver, in a way that conveys professional care and respect [11]. In addition to verbal communication, the pharmacist must also be aware of the messages conveyed through non-verbal communication, which can have a significant impact on the communication experience and can sometimes be more powerful than the verbal message itself. Adhering to principles and rules–such as demonstrating appropriate verbal, non-verbal, and paraverbal communication, practicing assertive communication, respecting personal space, and overcoming communication barriers–will contribute to effective communication with the patient in the community pharmacy [12, 13].

Nowadays, the notion of therapeutic communication is increasingly used. It involves the interpersonal transmission of information through words and behaviors, based on the knowledge, attitudes, and professional skills of the healthcare specialist, aimed at facilitating the patient's understanding and participation in making decisions about their health. Therapeutic communication techniques are specific methods used to provide patients with support and information, focusing on their concerns [14]. Applying therapeutic communication techniques for the pharmaceutical setting would enhance the image of the pharmacist as a medication specialist. Pharmacists can support patients in using medication–especially in outpatient settings–according to their needs, values, abilities, and specific characteristics. Depending on the patient category and their needs, appropriate terminology should be used to promote understanding and build a relationship of trust.

Lack of communication or ineffective communication is the most common cause of medication errors reported at all three levels: prescribing, dispensing, and administration [15, 16]. To minimize the impact of ineffective communication and ensure a correct and efficient communication process, healthcare providers can rely on the Guide on the Application of the Procedure for Patient Communication and Counseling, approved by the Order No. 425 of the Ministry of Health, Labor and Social Protection of the Republic of Moldova, dated March 20, 2018. This guide represents a valuable resource for professionals seeking to develop their patient counseling skills through the use of the described techniques and tools [17].

The study conducted by Stela Adauji (2023) highlights that „pharmacists possess verbal communication skills and are involved in the patient counseling process when dispensing medications, including those on the Rx list, through various methods. They also have the appropriate knowledge and skills to determine and assess the health problems of patients in the case of self-medication and can be involved

in monitoring these processes" [18]. The pharmaceutical care provided by pharmacists varies across different patient categories and depends on several factors, with age being one of the most significant. The characteristics of elderly individuals as medication consumers underscore the need for specialized pharmaceutical care [19, 20], especially through the lens of therapeutic communication in the community pharmacy, considering that pharmacists have previously viewed elderly patients as only partially communicative and unlikely to seek additional information [21].

In this context, **the aim of the study** was to highlight the principles and general rules adapted to support effective communication tailored to the needs of elderly individuals as beneficiaries of specialized pharmaceutical care and to ensure the quality of pharmaceutical services provided to them in the community pharmacy. Highlighting communication principles will provide support pharmacists in creating a favorable environment during counseling sessions with elderly and in meeting their needs and expectations.

Material and methods

The research conducted was descriptive in nature, with the research instrument being a questionnaire that included 8 closed-ended questions addressing aspects of information exchange between pharmacists and elderly patients during medication dispensing. The study involved a survey of 406 respondents, with the representative sample size calculated using Cochran's formula based on the following data: the number of pharmacists in 2023 according to the National Bureau of Statistics (BNS) – 1873, confidence level – 1.96, margin of error – 0.05, and estimated population proportion – 0.5. Thus, the corrected sample size for a population of 1873 pharmacists was approximately 319. Statistical analysis included the calculation of the confidence interval using Excel software. The methodological framework for analysis and the development of recommendations was based on the provisions of the Deontological Code of Pharmacists of the Republic of Moldova, the Good Pharmacy Practice Rules, the Deontological Code of Medical and Pharmaceutical Workers, and the Guide on the Application of the Procedure for Patient Communication and Counselling.

Results and discussions

The majority of pharmacist respondents identified doctors' or nurses' recommendations as the main sources about medications (81.5%, 95% CI: 77.75-85.30), followed by pharmacists' recommendations (70%, 95% CI: 65.49-74.41) (Fig. 1). Professional differences, as well as their place in the healthcare system, highlight the importance of each specialist in promoting the rational use of medication. They ensure that the recommended medication is appropriate for the patient and the condition they are suffering from. On the one hand, the fact that specialists remain the main source for choosing the elderly patient's medication contributes to reducing and avoiding many problems related to medication management. On the other hand, the fact that other sources of medication choice include medication advertising provided through various means (77.6%, 95% CI: 71.52-81.64), advice from others (66.5%, 95% CI: 61.91-71.09), family members' experiences (60.8%, 95% CI: 56.08-65.58), or television shows (56.2%, 95% CI: 51.33-60.98) highlights the need for effective communication between the specialist and the elderly patient. This ensures an objective level of information about medications and limits the influence of aggressive medication promotion. The concept of rational use of medications is a priority in the pharmaceutical system, and communication is the primary tool for promoting it.

In the case of the elderly, their ability to manage their own medications is influenced by the severity of their illness or illnesses and the treatment regimens, which are often complicated, thereby increasing the risk of medication misuse. Specialized pharmaceutical care, in this sense, aims to reduce the burden of polypharmacy typical among

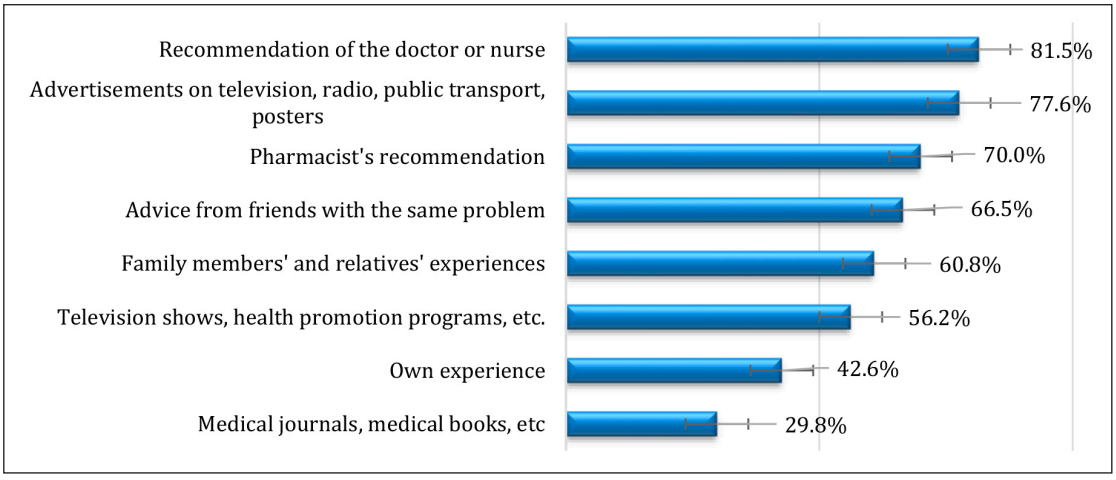

Fig. 1 The sources from which elderly patients gather information influencing their choice of medications.

Each source is represented as a percentage of the total responses. The data highlight the most to least influential sources: Medical journals, books, etc. (29.8%); Own experience (42.6%); Television shows and health promotion programs (56.2%); Family members' and relatives' experiences (60.8%); Advice from friends with similar conditions (66.5%); Pharmacist's recommendation (70.0%); Advertisements on television, radio, public transport, posters (77.6%); Recommendation of the doctor or nurse (81.5%).

the elderly by counseling and helping them understand how, when, and why to administer medication. Clear and accessible communication in this regard is indispensable. In their interactions with the elderly, pharmacists provide the informational support that the latter need, taking into account the vulnerability of elderly patients and their specific needs. The needs of the elderly are often determined by the deficiencies that arise with aging, such as memory loss, decreased visual and auditory acuity, decreased muscle strength and mobility, etc. For the communication process, these become barriers that the pharmacist must recognize and accommodate by adapting the information exchange to each individual patient.

Thus, the majority of respondents, 44.1% (95% CI: 39.25-48.91), indicated that they rarely encounter communication barriers with the elderly during counseling (Fig. 2). A smaller number, 29.3% (95% CI: 24.88-33.73), stated that they often do, and only 6.2% (95% CI: 3.81-8.49) – very often. Identifying and overcoming communication barriers in the pharmacist-elderly patient relationship depend on the techniques and tools applied by pharmacists in practice. In this sense, implementing a counseling algorithm for elderly patients in community pharmacies would have a significant impact on the quality of communication between them.

Furthermore, the majority of respondents indicated that often (47.4%, 95% CI: 42.43-52.14), the elderly had erroneous information about the requested medications; only 6.4% (95% CI: 4.02-8.78) indicated "very rarely", and 1.7% (95% CI: 0.45-2.99) – "never" (Fig. 3). Thus, open and effective communication, as well as adapting the language to the elderly's level of understanding, can make a difference in assimilating accurate information about medications provided in the community pharmacy.

When elderly individuals have erroneous information about the medications they are about to administer or do not receive complete and clear information about them from the specialist, the rate of administration errors in-

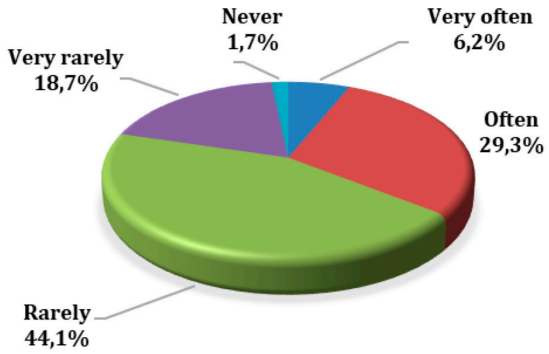

Fig. 2 Communication barriers experienced during counseling sessions with elderly patients.

Each category reflects the percentage of respondents who identified the respective frequency of these barriers: Very often: 6.2%; Often: 29.3%; Rarely: 44.1%; Very rarely: 18.7%; Never: 1.7%.

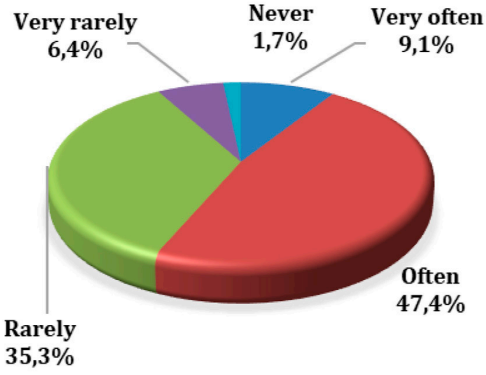

Fig. 3 Frequency of erroneous information elderly individuals had about requested medications

Each frequency category is represented as follows: Very often: 9.1%; Often: 47.3%; Rarely: 35.2%; Very rarely: 6.4%; Never: 1.7%.

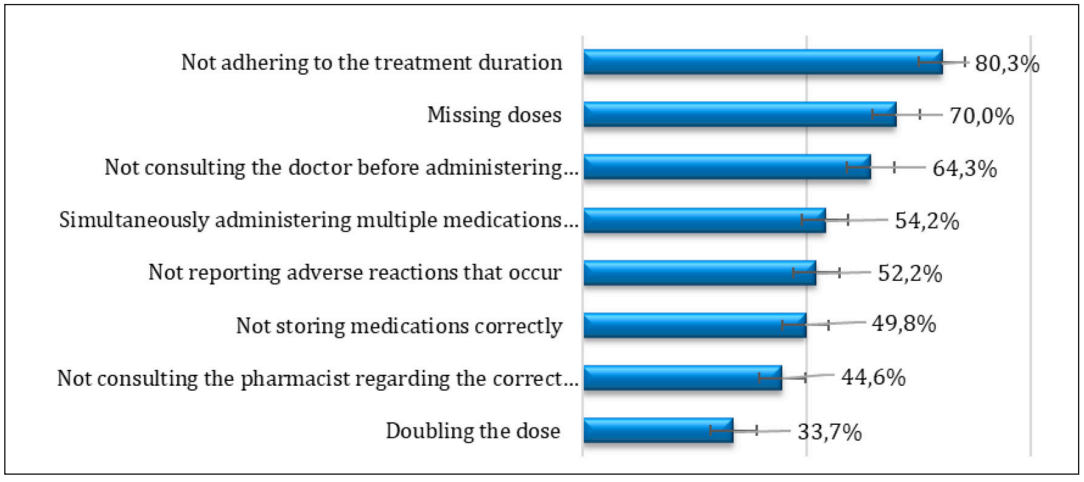

Fig. 4. Frequency of errors committed by the elderly regarding medication treatment, %.

Each error category is represented as follows: Not adhering to the treatment duration: 80.3%; Missing doses: 70.0%; Not consulting the doctor before administering medications: 64.3%; Simultaneously administering multiple medications from the same therapeutic group: 54.2%; Not reporting adverse reactions: 52.2%; Not storing medications correctly: 49.8%; Not consulting the pharmacist regarding correct administration: 44.6%; Doubling the dose: 33.7%.

creases. Responses provided by pharmacists indicate that the most common errors made by the elderly are related to not following the prescribed treatment duration (80.3%, 95% CI: 76.42-84.16), followed by missed doses (70.0%, 95% CI: 65.49-74.41) and administering medications without consulting the doctor or pharmacist and receiving the necessary recommendations (64.3%, 95% CI: 59.62-68.94) (Fig. 4).

To prevent medication errors, pharmacists are encouraged to ask elderly patients questions and to speak openly with them about any difficulties or uncertainties they may have regarding their medication. This helps build trust in the pharmacist and ensures that patients are properly informed about their treatment.

Thus, the majority of respondents indicated that they often (56.8%, 95% CI: 51.82-61.47) and very often (31.5%, 95% CI: 27.0-36.04) ask elderly individuals questions regarding the medications they administer (Fig. 5), and similarly about the ailments they suffer from (Fig. 6).

Pharmacists can structure interactions with patients by asking a series of open and closed questions, ideally starting with a broad open-ended question followed by a few specific closed questions, to find out about the medications and ailments the elderly suffer from and to engage them in the discussion. Pharmacists who avoid leading and loaded questions can ensure that the elderly feel comfortable and help create a pleasant environment. As a result, the latter will provide truthful information. In addition, pharmacists who ask elderly patients „why?" may appear critical and sometimes indifferent, which is why it is recommended that, instead of asking „why?", pharmacists request information using phrases such as, „Please, in your view, explain your decision to ...?". In this context, it is relevant that most pharmacists have indicated that the elderly ask various questions regarding the requested medications (Fig. 7).

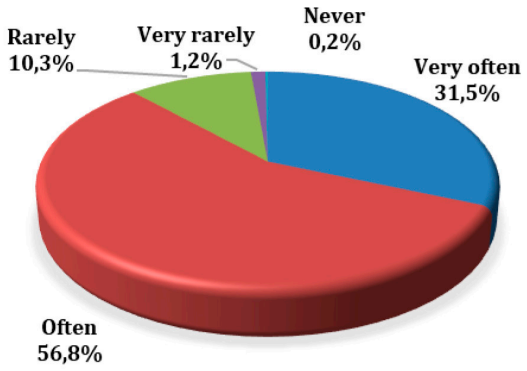

Fig. 5 The frequency of questions asked to elderly patients about the medications they take during their visit to the pharmacy.

The data is categorized as follows: Very often: 31.5%; Often: 56.7%; Rarely: 10.3%; Very rarely: 1.2%; Never: 0.2%.

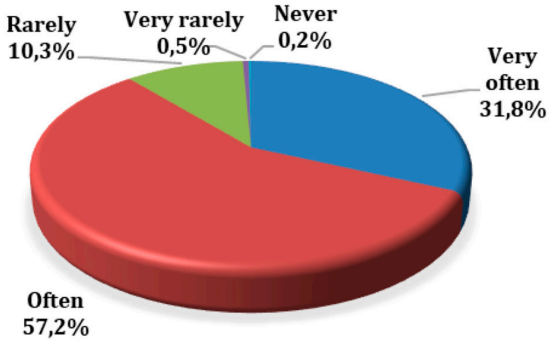

Fig. 6 The frequency of questions asked to elderly patients about the ailments they suffer from during their visit to the pharmacy.

The data is categorized as follows: Very often: 31.8%; Often: 57.2%; Rarely: 10.3%; Very rarely: 0.5%; Never: 0.2%.

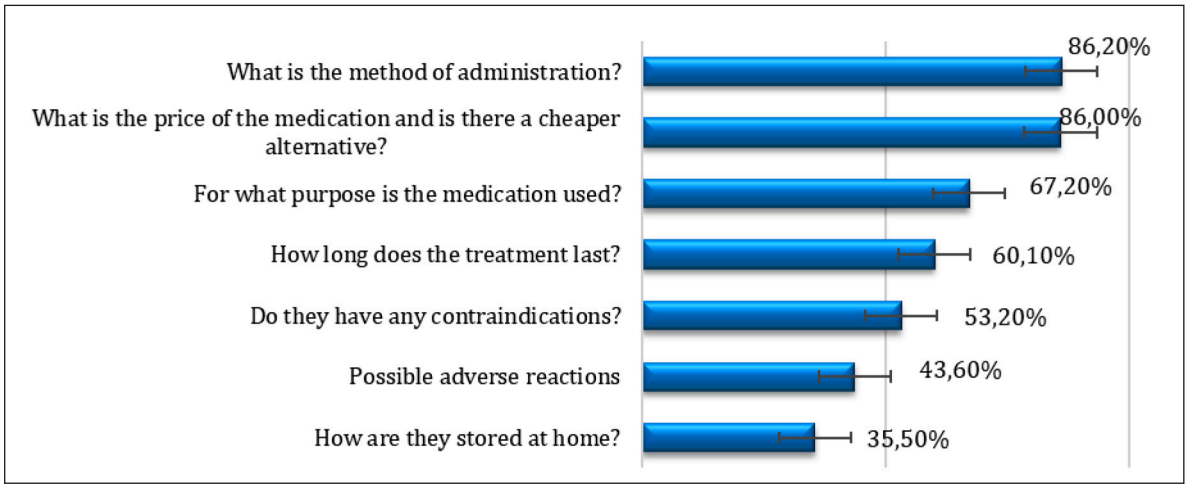

Fig. 7 Type of questions asked by the elderly to pharmacists regarding the requested/dispensed medications, %.

Each question type is represented as follows: What is the method of administration? 86.2%; What is the price of the medication and is there a cheaper alternative? 86.0%; For what purpose is the medication used? 67.2%; How long does the treatment last? 60.1%; Do they have any contraindications? 53.2%; Possible adverse reactions: 43.6%; How are they stored at home? 35.5%.

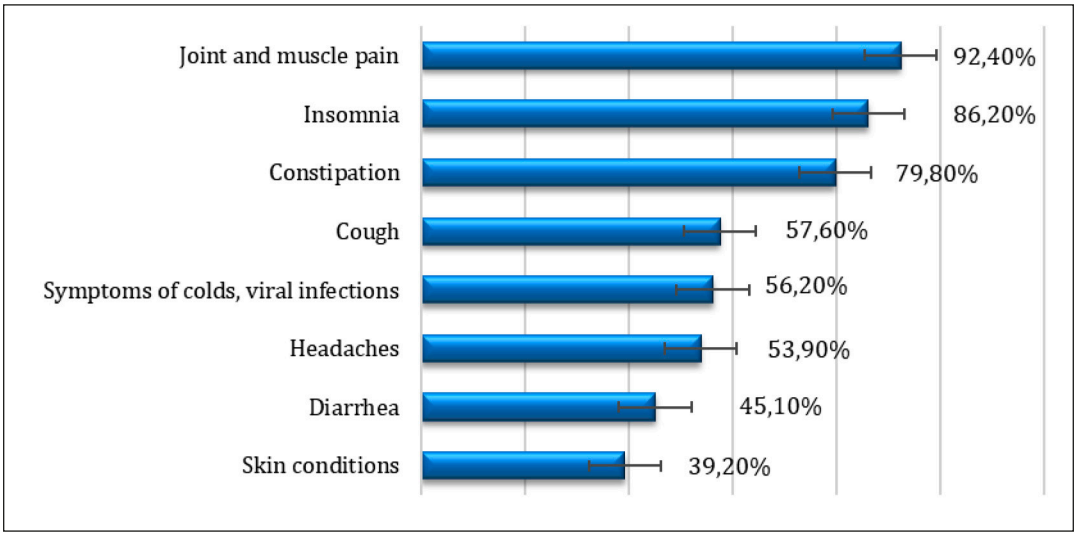

Fig. 8 Ailments/symptoms for which the elderly seek the pharmacist's advice, %.

Each condition is represented by the following percentages: Joint and muscle pain: 92.4%; Insomnia: 86.2%; Constipation: 79.8%; Cough: 57.6%; Symptoms of colds and viral infections: 56.2%; Headaches: 53.9%; Diarrhea: 45.1%; Skin conditions: 39.2%.

Thus, community pharmacists can assert their position as the primary specialist in the field of medication and provide pharmaceutical care based on medication therapy management: educate elderly patients about dispensed medications, prevent drug interactions and polypharmacy, increase treatment adherence, and collect information about adverse drug reactions, etc.

Interaction with elderly patients in the community pharmacy has many challenges, but also opportunities. Besides focusing on pharmacists ensuring that patients understand the treatment regimens recommended by doctors, an important aspect is also establishing treatment plans for minor ailments. In this case, pharmacists are the ones who recommend and select over-the-counter medications suitable for the elderly patient. Respondents indicated that the elderly ask them for advice regarding the treatment of ailments such as muscle pain (92.4%, 95% CI: 89.78-94.94), insomnia (86.4%, 95% CI: 82.85-89.56), constipation (79.8%, 95% CI: 75.89-83.70), and cough (57.6%, 95% CI: 52.82-62.44), etc. (Fig. 8).

The application of effective communication principles allows for providing the elderly with the necessary information regarding the medication for these minor ailments. Nonverbal components, including eye contact, smiling, posture, the presence or absence of privacy space, and external appearance, are important for effective communication and properly guiding the elderly about the ailments they suffer from. Verbal communication should also be carefully controlled and designed by the pharmacist. Verbal components, such as reflective listening, asking questions, referencing, and using appropriate terminology, can greatly influence the success of a conversation with elderly patients.

Empathy conveyed through smiling, a warm voice, head tilting, and eye contact is correlated with increased receptiveness and information sharing from elderly patients. Additionally, applying standardized communication techniques, such as a counseling algorithm centered on the elderly patient, would allow for correct and rational decision-making about their medication, especially in cases of minor ailments.

Conclusions

1. An analytical synthesis of the literature on communication principles was conducted, and those necessary for application in the process of counseling patients in community pharmacies were highlighted.

2. The principles and communication rules that must be followed in specialized geriatric pharmaceutical care have been highlighted.

3. The counseling algorithm for geriatric patients in the community pharmacy was developed based on the results obtained from surveying pharmacists, which will be included in the guide for the management of specialized pharmaceutical care for high-risk patients.

Competing interests

None declared.

Ethics approval

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemiţanu* State University of Medicine and Pharmacy (minutes No. 52 to 62, from 18.06.2015).

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RESEARCH ARTICLE

Assessment of osteoarticular morbidity in regions with different boron concentrations in deep drinking water of the Republic of Moldova

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ABSTRACT

Introduction. Even if boron is not yet recognized as an essential element for the human body, its insufficient intake is considered harmful, especially for the osteoarticular system. A daily intake of at least 3 mg of boron can fortify bone mass and prevent the onset of osteoarthritis, rheumatoid arthritis, and osteoporosis. This research aims to assess the morbidity caused by rheumatoid arthritis and inflammatory polyarthropathies in the population from regions with different boron concentrations in deep drinking water of the Republic of Moldova.

Material and methods. Two full-length descriptive observational studies were conducted: one on osteoarticular morbidity caused by rheumatoid arthritis and inflammatory polyarthropathies (incidence and prevalence), and one on boron concentrations in deep drinking water (public wells and artesian wells). Following national regulations, the Republic of Moldova was divided into three distinct boron-related areas, and in each of them, the boron trend overlapped with the morbidity trend.

Results. In the below-the-limit boron area, the research hypothesis was confirmed in two out of three districts, by overlapping osteoarticular morbidity with boron concentrations in deep drinking water and their trendlines. In the limit-level boron area, boron concentrations in drinking water do not appear to influence the studied osteoarticular morbidity in either district. In the above-the-limit boron area, unlike in previous research, trends for boron concentrations in public wells and artesian wells were opposite to those of the incidence and prevalence of rheumatoid arthritis and inflammatory polyarthropathies, confirming the research hypothesis.

Conclusions. Out of the three studied areas, the expected phenomenon of low morbidity and high boron concentrations, and vice versa, was observed in two below-the-limit boron districts and two above-the-limit boron districts. The results can be expanded upon in further research in the field.

Keywords: boron, osteoarticular diseases, deep drinking water, osteoarthritis, rheumatoid arthritis.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

No study has been conducted to link specific osteoarticular morbidity with the boron concentrations in deep drinking water from the Republic of Moldova. Moreover, in previous national reports on boron concentrations in drinking water, this trace element was addressed as a contaminant that should be reduced in the water consumed. This paper examines boron from the perspective of a bone and joint health enhancer.

The research hypothesis

Periods of higher boron consumption through deep drinking water by the population, showing a positive trendline, are accompanied by a lower incidence and prevalence of rheumatoid arthritis and inflammatory polyarthropathies, which show a negative trendline–and vice versa.

The novelty added by the manuscript to the already published scientific literature

The study offers a new perspective on how boron could be addressed in national regulations concerning drinking water and recommends raising its permissible limit to align with the EU standard for the benefit of the population. The characterization of regions with different boron concentrations in deep drinking water can be used to estimate the impact of this mineral on other body systems in future research.

Introduction

Boron is a trace element that has not yet been recognized as essential for the human body. The World Health Organization (WHO) highlights that insufficient boron intake can impair the body's biological functions, potentially causing long-term harm [1]. The WHO recommends drinking water as the primary source of this element and prioritizing natural springs rich in boron [2].

A minimum intake of 0.4 mg of boron per day can contribute to the strengthening of bone mass, with the regulated boron concentration in drinking water providing the body with basic essential benefits [2, 3]. Moreover, an adequate boron intake can reduce calcium and magnesium loss through urine [4, 5], promote osteogenesis [3, 6], decrease inflammatory joint processes [7, 8], reduce articular discomfort, and improve mobility [4, 9]. Osteoarticular diseases that can be prevented by a boron-rich diet include osteoarthritis, rheumatoid arthritis, and osteoporosis [10-12]. Recent research shows positive effects of boron on bone mass when the daily intake is 3 mg or more [5, 13, 14].

Population studies conducted more than three decades ago revealed that the incidence of arthritis was negatively associated with boron concentrations in soil and foods. Thus, in areas where the population's daily boron intake was below 1 mg/day, the arthritis incidence ranged from 20 to 70%, while in regions where it was 3-10 mg/day, the incidence of this pathology was between 0 and 10% [4]. Since those findings, no other population study of comparable scale has been conducted.

Following the previous national report, in the southern region of the Republic of Moldova, in Administrative Territorial Unit Gagauzia, drinking water is richest in boron, with concentrations reaching up to 3 mg/l. These results have not yet been linked with the population's health status [15]. Considering the lack of research on boron's impact on public health in our country, and the fact that osteoarticular diseases are the most studied in relation to daily boron intake, this association was chosen for our study.

Even though European regulations have set a limit of 1,5 mg/L of boron in drinking water and mention that this parameter can be raised to 2.4 mg/L in boron-rich areas [16], in our country, the maximum allowable boron concentration in drinking water is 1 mg/L [17]. Another justification for this research is to provide arguments for aligning national regulations on boron concentrations in drinking water with European standards.

This study aims to assess the morbidity caused by rheumatoid arthritis and inflammatory polyarthropathies in the population from regions with different boron concentrations in deep drinking water (public wells and artesian wells) of the Republic of Moldova.

Material and methods

To achieve the intended purpose, two full-length descriptive observational studies were conducted: one on osteoarticular morbidity and one on boron concentrations in deep drinking water.

The first step involved conducting a full-length descriptive observational study on osteoarticular morbidity (incidence and prevalence) caused by rheumatoid arthritis and inflammatory polyarthropathies during the period 2016-2020 (Table 1).

The results were analyzed and presented for the group of rheumatoid arthritis and inflammatory polyarthropathies as a whole. According to the International Statistical Classification of Diseases and Related Health Problems, Eleventh Revision (ICD-11), the group includes nine diseases, their codes being included between FA20 and FA27 and FA2Z.

Table 1. A brief description of the first full-length descriptive observational study on osteoarticular morbidity

Criteria	Description
Object of study	Adult morbidity due to rheumatoid arthritis and inflammatory polyarthropathies
Source of information	Data from the Health Data Management Department of the National Agency for Public Health
Collection method	Data processing, calculation of multiannual averages
Volume	A comprehensive study covering the period 2016-2020
Place of performance	National Agency for Public Health

During *the second step*, a full-length descriptive observational study on boron concentrations in deep drinking water–from public wells and artesian wells–covering the 2015-2022 period was conducted (Table 2).

The main argument of including water from public wells into our study was that this water source is frequently used by the rural population, which according to the National Bu-

reau of Statistics in 2017 constitutes 57.1% of the country's population and is a representative part of this research.

Table 2. A brief description of the second full-length descriptive observational study on boron concentrations in deep drinking water

Criteria	Description
Object of study	Boron concentrations in water from public wells and artesian wells across the territory of the Republic of Moldova
Source of information	Data from territorial Public Health Centers (2015-2020)
Collection method	Data processing, calculation of annual and multiannual averages
Volume	A comprehensive study for the period 2015-2020, with 2,706 samples investigated
Place of performance	National Agency for Public Health

Of the 2706 samples investigated, 480 were public well water and 2226 were artesian well water. The results were taken from the registers of territorial public health centers for the period 2015-2020. All available results from both sources were analyzed. Most samples were collected during the late summer-autumn period (August-November) or during spring (March-April). For artesian well water, for each locality, at least one sample from each artesian well has been collected per year, and the majority of them were analyzed for boron concentrations. For public well water, samples were collected less often, with an average periodicity of 1-3 samples analyzed for boron concentrations in 6 years, and not for all researched localities.

Given the national regulations restrict the boron concentrations in deep drinking water to 1 mg/L, the territory of the Republic of Moldova was divided into three distinct areas:

- *Below the limit* – boron concentrations between 0 and 0.8 mg/L;
- *Limit* –boron concentrations between 0.9 and 1.2 mg/L;
- *Above the limit* – boron concentrations above 1.2 mg/L.

From the available data, the most representative districts for each area were selected – for below the limit districts – districts with average values close to the lower limit, for districts in the limit area – average values close to the limit of 1 mg boron/l and for above the limit districts - maximum average values recorded in the country. Both public wells and artesian wells values were taken into consideration, but one of the two values for each district was the basis for the selection.

Following these criteria, selected districts for each boron-related area are:

- *Below the limit* area:
  - Călărași: 0.2 mg B/L in public wells;
  - Briceni: 0.25 mg B/L in artesian wells;
  - Drochia: 0.3 mg B/L in public wells.
- *Limit* area:
  - Cahul: 0.9 mg B/L in artesian wells;
  - Vulcănești: 1.1 mg B/L in artesian wells.
- *Above the limit* area:
  - Ceadîr-Lunga: 1.8 mg B/L in public wells;
  - Comrat: 1.43 mg B/L in artesian wells.

In the *final stage*, boron concentrations in deep drinking water and adult morbidity due to rheumatoid arthritis and inflammatory polyarthropathies were graphically overlaid for each selected district, and trendlines for both boron concentrations and osteoarticular morbidity were calculated using Microsoft Excel 2021.

Statistical data processing: For the prevalence data of adults with rheumatoid arthritis and inflammatory polyarthropathies, the average prevalence for the research period was calculated. Boron concentration data in deep drinking water were organized into two separate databases: one for public wells and another for artesian wells. Average boron concentrations were calculated separately for each village and district, including the Administrative Territorial Unit Gagauzia, on a yearly basis. Subsequently the total average concentration for the analyzed period was determined for each district. Microsoft Excel 2021 was used for database creation and calculations of all averages.

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes No 1 of 07.09.2020).

Results

The below-the-limit boron in deep drinking water refers to multiannual averages of boron concentration between 0 and 0.8 mg/L.

In the Călărași district, in 2020, when the boron concentrations in public wells and artesian wells reached their highest levels during the research period, the prevalence of rheumatoid arthritis and inflammatory polyarthropathies recorded its lowest values. The upward trend in boron concentrations in deep drinking water ($y = 0.06x + 0.3825$ for artesian wells water and $y = 0.0442x + 0,0654$ for public wells water) overlapped with a downward trend in the prevalence of rheumatoid arthritis and inflammatory polyarthropathies among adults during the 2016-2020 period ($y = -1,48x + 35.78$) which supports the research hypothesis (Figure 1).

In Briceni, in 2018, both the prevalence and incidence of adults with rheumatoid arthritis and inflammatory polyarthropathies increased against the background of a decrease in boron concentrations in water from public and artesian wells. The trends for boron concentrations in artesian wells ($y = -3.25x + 28.65$), as well as for the incidence ($y = -0.18x +3.85$) and prevalence ($y = -0.055x +0.375$) of rheumatoid arthritis and inflammatory polyarthropathies in adults, were all decreasing (Figure 2). Although the trendlines for boron concentrations in deep drinking water and adult morbidity do not support the research hypothesis, the increase in prevalence and incidence coincides with the decrease in boron concentrations in artesian wells.

In the Drochia district, in 2020, boron concentrations in deep drinking water, as well as osteoarticular morbidity, reached their maximum values for the analyzed period. Additionally, the trends for boron concentrations in arte-

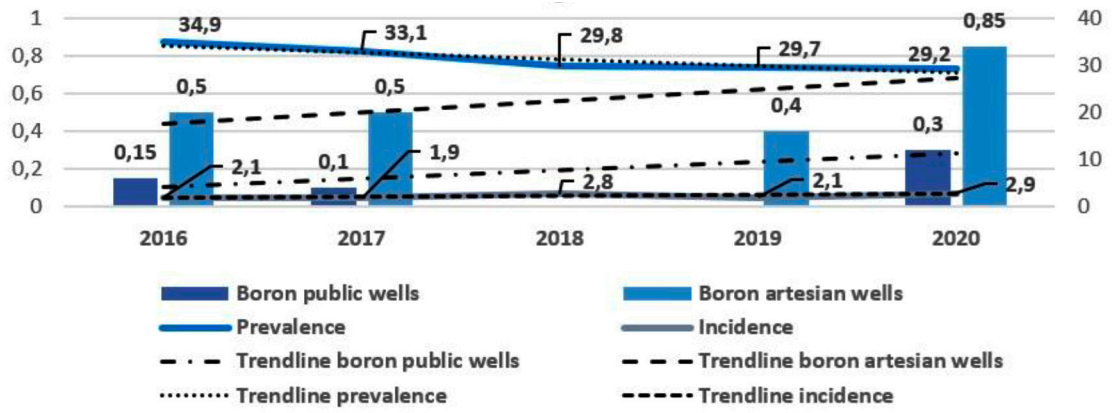

Fig. 1 Boron concentrations in deep drinking water (mg/L) and adult morbidity from rheumatoid arthritis and inflammatory polyarthropathies (per 10,000 inhabitants), Călărași district, 2016-2020

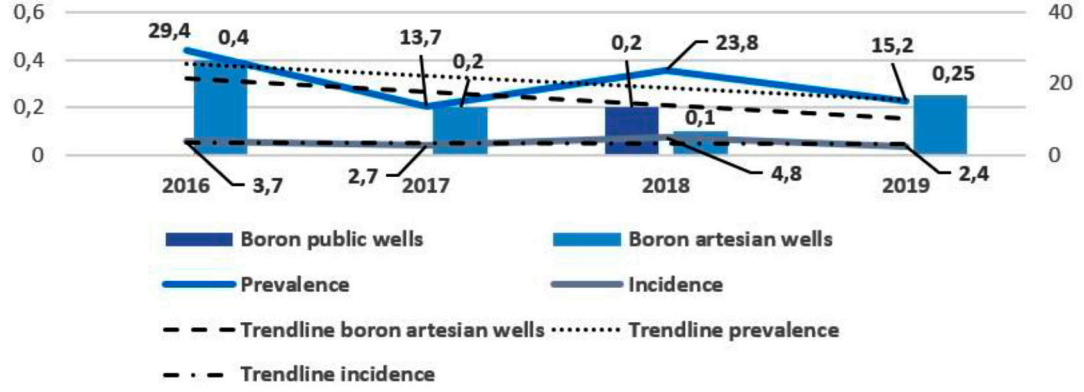

Fig. 2 Boron concentrations in deep drinking water (mg/L) and adult morbidity from rheumatoid arthritis and inflammatory polyarthropathies (per 10,000 inhabitants), Briceni district, 2016-2019

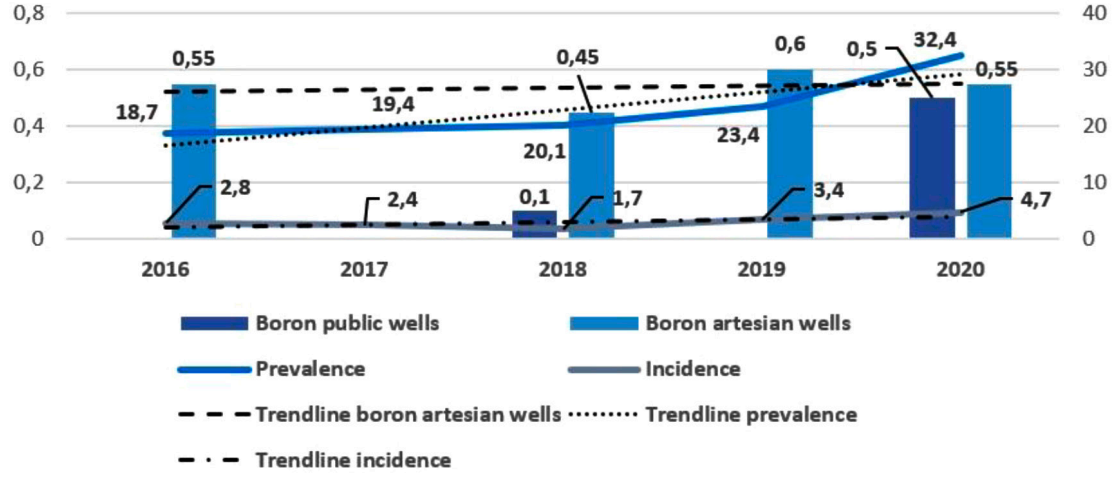

Fig. 3 Boron concentrations in deep drinking water (mg/L) and adult morbidity from rheumatoid arthritis and inflammatory polyarthropathies (per 10,000 inhabitants), Drochia district, 2016-2020

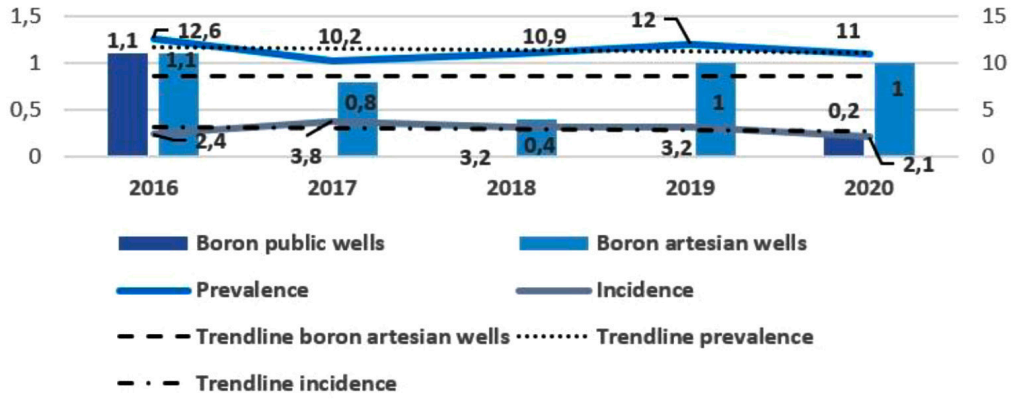

Fig. 4 Boron concentrations in deep drinking water (mg/L) and adult morbidity from rheumatoid arthritis and inflammatory polyarthropathies (per 10,000 inhabitants), Cahul district, 2016-2020

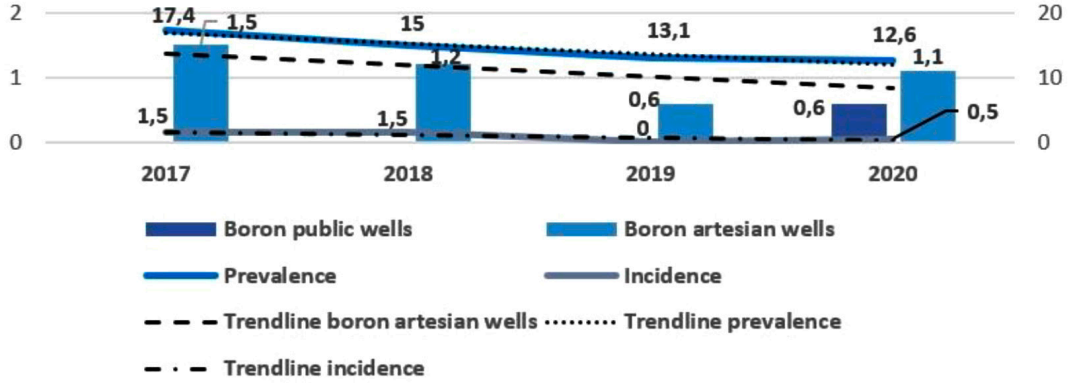

Fig. 5 Boron concentrations in deep drinking water (mg/L) and adult morbidity from rheumatoid arthritis and inflammatory polyarthropathies (per 10,000 inhabitants), Vulcăneşti district, 2017-2020

sian well water (y = 0.0071x + 0.5143) and prevalence from rheumatoid arthritis and inflammatory polyarthropathies (y = 3.14x + 13.38) were both positive (Figure 3). Neither the trendlines for boron concentrations in deep drinking water and osteoarticular morbidity nor of the year-by-year overlap between boron concentrations and incidence/prevalence support the research hypothesis.

Limit-boron in the deep drinking water area (multiannual averages of boron in deep drinking water between 0.9 and 1.2 mg/L)

In the Cahul district, in 2016, when the boron concentration in water from public wells and artesian wells reached its highest levels, the prevalence of adults with rheumatoid arthritis and inflammatory polyarthropathies also reached a maximum, while the incidence was at its lowest for the 2016-2020 period. Trendlines for boron concentrations in deep drinking water (y = -3E-16x + 0.86 for boron concentrations in artesian wells) and osteoarticular morbidity (-0.14x + 11.76 for the prevalence and y = -0.12x +3.3 for the incidence) were both negative (Figure 4). The overlap of high boron concentrations in public and artesian wells with the incidence values matches the research hypothesis, while the trendlines for boron and morbidity do not.

In the second district with limited boron concentration in deep drinking water, Vulcăneşti, during the years with the highest boron concentrations in public well water (2017-2018), both the prevalence and the incidence of adults with osteoarticular pathologies were at their highest. Additionally, the trends for boron concentrations in artesian wells (y = -0.18x +1.55) and morbidity values (y=-1.63x +18.6 for the prevalence and y = -0.45x +2 for the incidence) were negative (Figure 5). The overlapping of boron concentrations in artesian wells and annual osteoarticular morbidity, as indicated by the trendlines equations, is opposite to the research hypothesis.

Above-the-limit boron in deep drinking water area (multiannual averages of boron in deep drinking water above 1.2 mg/L)

Boron concentrations in deep drinking water and morbidity indicators in the Ceadîr-Lunga district show that prevalence values for rheumatoid arthritis and inflammatory polyarthropathies increased during the period when boron concentration in deep waters was decreasing (2018-

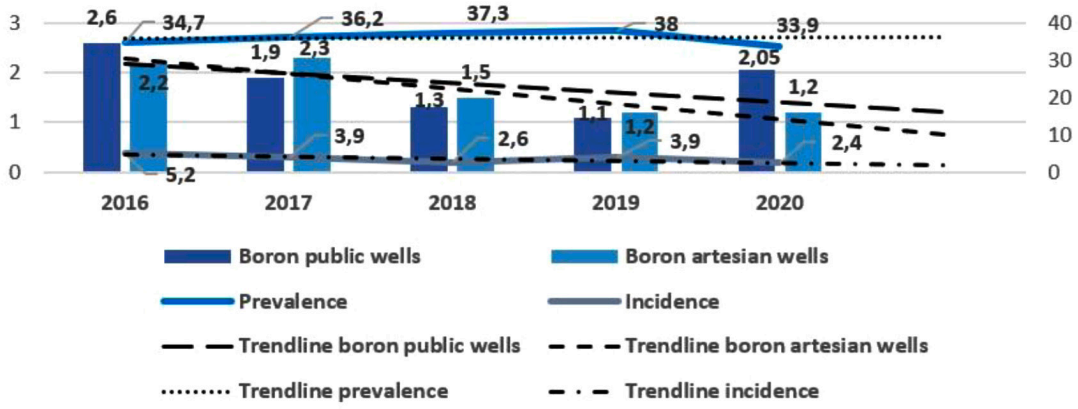

Fig. 6 Boron concentrations in deep drinking water (mg/L) and adult morbidity from rheumatoid arthritis and inflammatory polyarthropathies (per 10,000 inhabitants), Ceadîr-Lunga district, 2016-2020

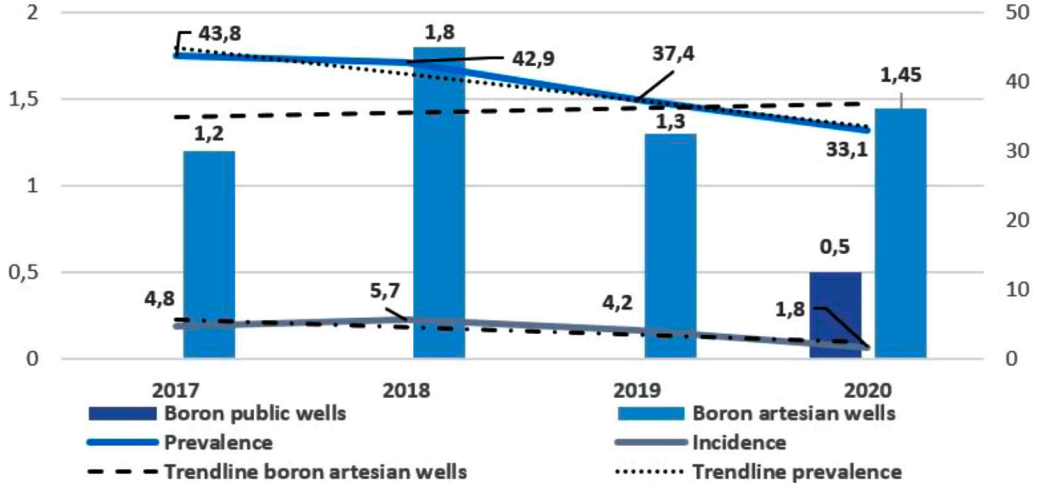

Fig. 7 Boron concentrations in deep drinking water (mg/L) and adult morbidity from rheumatoid arthritis and inflammatory polyarthropathies (per 10,000 inhabitants), Comrat district, 2017-2020

2019). Trends in boron concentrations were negative (y = -0.19x + 2.36 for public wells water and y = -0.31x + 2.61 for artesian wells water), while prevalence of rheumatoid arthritis and inflammatory polyarthropathies showed positive trends (y = 0.02x +35.96) (Figure 6).

In the second selected above-the-limit district, Comrat, increasing boron concentrations in artesian wells water trendline (y = 0.025x + 1.375) coincided with decreasing trends in osteoarticular morbidity (y=-3.76x + 48.7 for the prevalence and y = -1.05x + 6.7 for the incidence) (Figure 7). Although osteoarticular morbidity remains high during periods of elevated boron concentrations in artesian wells, the opposing trendlines for incidence and prevalence compared to boron concentrations support the research hypothesis.

Discussion

During this research, we compared the annual averages of boron concentrations in deep drinking water (from public and artesian wells) with annual averages of incidence and prevalence of rheumatoid arthritis and inflammatory polyarthropathies in selected districts from each boron-related area, using periods when all relevant data were available. Additionally, we calculated trends for all four indicators – boron concentrations in public well water and artesian wells water, and incidence and prevalence of rheumatoid arthritis and inflammatory polyarthropathies. The aim of this study was to assess whether boron concentrations in deep drinking water can influence osteoarticular morbidity in specific regions, based on existing literature [2-14].

In the below-the-limit boron area of deep drinking water, the Călăraşi district showed fluctuations in boron concentrations from public and artesian wells that corresponded with the prevalence of adults with rheumatoid arthritis and inflammatory polyarthropathies, consistent with the research hypothesis. This is further supported by the increasing boron and decreasing morbidity trends. Similarly, in the Briceni district, the hypothesis is confirmed by the

overlap of boron concentrations in deep drinking water and the osteoarticular morbidity indicators in adults, along with matching trends across the four indicators. However, in the Drochia district, the research hypothesis was not confirmed.

In the limit-boron area of deep drinking water, the research hypothesis was only partially confirmed in the Cahul district, and only by the incidence of the studied diseases in a single year of the study period; however, the overall trendlines did not align with the hypothesis. In Vulcănești, neither the boron concentrations in deep drinking water nor the morbidity of adults with the studied osteoarticular pathologies corresponded with the research hypothesis, and the trendlines for the three indicators also failed to match it.

In the above-the-limit boron area of deep drinking water, the research hypothesis was largely confirmed in the Ceadîr-Lunga and Comrat districts, where the boron concentrations and their trendlines overlapped with the annual averages and trendlines of morbidity, demonstrating the expected relationship.

The described results complement previously published findings, which showed that in the above-the-limit boron area of deep drinking water in the southern region of the Republic of Moldova, the multiannual averages of rheumatoid arthritis and inflammatory polyarthropathies prevalence were the highest in the country [18]. However, analyzing annual averages instead of multiannual ones, and calculating trends for both boron concentrations and osteoarticular morbidity, revealed mixed results and provided a different perspective on the boron-rich areas.

The limitations of this research include incomplete data on boron concentrations in deep drinking water, particularly for public wells, which were not available for every year. Additionally, morbidity data were only available up to 2020, resulting in differences in the analyzed periods between districts. Furthermore, it was not possible to separate rheumatoid arthritis from other inflammatory polyarthropathies, as the Health Data Management Department provided combined data. Consequently, some results may be influenced by the inclusion of various inflammatory pathologies in the statistics. For the same reason, studying the association with osteoarthritis was not feasible, as it was grouped with other chondropathies.

Taking these aspects into consideration, we believe that future investigations focusing specifically on the association between boron concentrations in deep drinking water and the separate conditions of rheumatoid arthritis and osteoarthritis could be a valuable direction.

Conclusions

The overlap of trends in boron concentrations in deep drinking water and trends in adult morbidity from rheumatoid arthritis and inflammatory polyarthropathies confirmed the research hypothesis in the above-the-limit boron area (Ceadîr-Lunga and Comrat districts) and partially in the below-the-limit boron area (Călărași and Briceni districts). These results provide a foundation for future research on the impact of boron on public health.

Competing interests

None declared.

Authors' contributions

MVR conceived the study and drafted the manuscript, IP participated in the study design and data analysis, EC helped draft the manuscript and contributed to the study design, and LMN performed statistical analysis of clinical data. All authors have read and approved the final version of the manuscript.

Ethics approval

The study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes No 1 of 07.09.2020).

Patient consent

Obtained.

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REVIEW ARTICLE

The role of autoantibodies in neuropsychiatric systemic lupus erythematosus: mechanisms, biomarkers and clinical correlations

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ABSTRACT

Introduction. Neuropsychiatric lupus erythematosus is still a disease with a very challenging diagnostic process, lacking high specificity and sensitivity assays. Autoantibodies can change this perspective, and because of their pathogenetic involvement, can become a very powerful tool for early detection and disease activity tracking. However, their biomarker potential still needs further evaluation. In this study, we focused on the pathogenetic mechanisms of neuropsychiatric lupus erythematosus and the involvement of brain-specific and systemic autoantibodies in the development of neuropsychiatric manifestations.

Material and methods. Medical articles addressing the correlation of autoantibodies concentrations in serum and cerebrospinal fluid and their potential pathogenetic mechanism, were reviewed. More than 100 articles were identified from databases such as PubMed, ScienceDirect, Frontiers, and Wiley, using keywords such as "neuropsychiatric lupus erythematosus", "autoantibodies", "pathogenesis", "biomarker" and "neuropsychiatric manifestations". From these, 47 articles were selected for the current review.

Results. Autoantibodies truly are indeed a tool in the diagnostic process of neuropsychiatric lupus erythematosus, and many researchers have obtained statistically valid correlations between their presence and specific neuropsychiatric manifestations. Variations in their concentration not only reflect the disease activity but also the fact that they are involved in its development through interactions with neuronal and vascular targets. Besides autoimmunity, brain-blood barrier dysfunction is also another key part of the pathogenetic mechanism, with markers of this injury also being useful in the diagnostic methodology. With future research, specific combinations of these markers can be linked to distinct clinical manifestations by creating multi-biomarker panels, a robust framework for diagnosing neuropsychiatric lupus erythematosus.

Conclusions. Neuropsychiatric lupus erythematosus remains a condition that highly challenging to diagnose and manage due to the heterogeneity of symptoms and the lack of standardized diagnostic tools. Autoantibodies, along with other markers of vascular and inflammatory injury can aid specialists in dealing with this disease, but further research is needed to validate these biomarkers in diverse patient populations and to standardize assays for clinical application to improve the early detection and management of NPSLE, ultimately enhancing patient outcomes and quality of life.

Keywords: neuropsychiatric lupus erythematosus, pathogenesis, autoantibodies, brain-blood barrier, neuro-inflammation, biomarker.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Despite extensive research, the precise pathogenetic role and diagnostic utility of many brain-specific autoantibodies in neuropsychiatric systemic lupus erythematosus remain unclear. Additionally, there is limited understanding of how disruptions in the blood-brain barrier and its interaction with these autoantibodies can be reliably measured and integrated into personalized therapeutic strategies.

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The research hypothesis

Specific brain-targeted autoantibodies and disruptions in the blood-brain barrier play a pivotal role in the pathogenesis of neuropsychiatric systemic lupus erythematosus, offering potential as biomarkers and therapeutic targets for personalized management.

The novelty added by the manuscript to the already published scientific literature

The manuscript highlights the potential of specific brain-targeted autoantibodies and blood-brain barrier disruptions as combined biomarkers for neuropsychiatric systemic lupus erythematosus, emphasizing their role in symptom-specific pathogenesis and paving the way for personalized diagnostic and therapeutic strategies.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by a loss of immune tolerance, the production of autoantibodies against self-antigens, and the formation of immune complexes that contribute to inflammation and tissue damage [1, 2]. Affecting multiple organ systems, SLE commonly involves the skin, joints, kidneys, and serosal membranes. The disease's considerable heterogeneity, influenced by genetic, environmental, and immunological factors, has earned the title "the disease with a thousand faces". Among its many manifestations, involvement of the central and peripheral nervous systems represents a unique and complex aspect of the disease, known as neuropsychiatric systemic lupus erythematosus (NPSLE).

NPSLE is defined as a set of neuropsychiatric manifestations that can affect both the central and peripheral nervous system and encompasses a spectrum ranging from mild cognitive impairments and anxiety to severe manifestations, including stroke, seizures, and psychosis [2-4]. These symptoms can be classified as primary, if the manifestation is a result of the autoimmune inflammatory processes from the nervous system, or secondary due to the treatment or infections of the nervous system from chronic immunosuppression. Also, they can be divided into focal or diffuse manifestations, and central or peripheral, depending on what part of the nervous system is affected [2].

The clinical manifestations can vary from patient to patient, ranging from headaches and subtle cognitive dysfunction to more severe manifestations, including psychosis, acute confusion, and epilepsy. According to the American College of Rheumatology nomenclature and classification criteria, scientists identified 12 neuropsychiatric manifestations associated with the central nervous system (CNS) and 7 associated with the peripheral nervous system [3-5] (Table 1). Some of these symptoms are seen more frequently (cognitive dysfunction, mood disorders, anxiety headaches, seizures) whereas others remain infrequent or very rare (acute confusional status, aseptic meningitis, autonomic disorders, plexopathy) [3].

Table 1. Classification of neuropsychiatric and neurological syndromes in NPSLE according to ACR criteria [4].

Category	Central Nervous System	Peripheral Nervous System
Neurological Syndromes	Focal Manifestations Seizure disorders Aseptic meningitis Demyelinating syndromes Myelopathy Cerebrovascular disease Headache Movement disorders	Focal Manifestations Autonomic disorders Myasthenia gravis Polyneuropathy Cranial neuropathy Guillain-Barré syndrome (GBS) Mononeuropathy Plexopathy
Neuropsychiatric Syndromes	Diffuse Manifestations Anxiety disorders Psychosis Acute confusional state Cognitive dysfunction Mood disorders	

***Note**: This table presents the classification of neuropsychiatric and neurological manifestations in neuropsychiatric systemic lupus erythematosus (NPSLE) as defined by the American College of Rheumatology (ACR). The manifestations are categorized based on their association with the central nervous system (CNS) or peripheral nervous system (PNS), and are further divided into focal and diffuse syndromes. While some manifestations, such as cognitive dysfunction and mood disorders, are commonly observed, others like acute confusional states and plexopathies are infrequent or rare.*

One of the major challenges in dealing with NPSLE patients is determining whether the neuropsychiatric manifestations are attributable and result directly from SLE, or are consequences of factors such as treatment, comorbid conditions, or non-organic psychological diseases that mimic the neuropsychiatric symptoms of the SLE. Along with the American College of Rheumatology definitions, Bortoluzzi *et al.* proposed and validated an algorithm based on lupus activity assessment, imaging techniques, and cerebrospinal fluid analysis to better differentiate the primary NPSLE manifestations from those caused by other factors [6, 7]. Also based on different SLICC inception cohort studies, researchers have also developed additional criteria to consider in the evaluation of NPSLE manifestations. These criteria take into account critical factors such as the temporal relationship between the interval of the

onset of neuropsychiatric symptoms and the diagnosis of SLE, the presence of secondary causes for the NPSLE-like manifestations, and the frequency of particular neuropsychiatric events in the general population. Also, according to these criteria, symptoms such as isolated headaches, mild anxiety or depression, and cognitive impairment affecting fewer than three cognitive domains are less likely to be attributed to SLE [3-5].

Despite advancements in understanding NPSLE, significant challenges remain in its recognition, diagnosis, and treatment due to the heterogeneity of symptoms, the absence of standardized diagnostic criteria, and the limited reliability of conventional markers [4, 6, 8]. Among the promising avenues for addressing these gaps is the exploration of autoantibodies as biomarkers for NPSLE. Brain-targeting autoantibodies, such as anti-NMDA receptor and anti-ribosomal P protein antibodies, have been implicated in both serum and cerebrospinal fluid (CSF) of NPSLE patients, with their presence often correlating with specific neurological manifestations and blood-brain barrier (BBB) disruption [2, 5, 9]. These autoantibodies, along with others targeting phospholipids or unidentified CNS antigens, provide a potential window into the mechanisms of NPSLE and its clinical variability. This research aims to explore their role as biomarkers, highlighting their diagnostic and prognostic utility while investigating the underlying pathogenesis, particularly the role of BBB leakage.

Material and methods

A comprehensive literature review was conducted to analyze the role of antibodies in the pathogenesis, diagnosis, and prognosis of NPSLE, with a specific focus on their utility as biomarkers and their involvement in the neuroinflammatory process. This section describes the methodological approach used to identify, analyze, and synthesize relevant studies, ensuring a thorough and critical examination of the existing knowledge base.

Data sources and search strategy. The systematic search spanned multiple databases, including PubMed, Frontiers, Springer Nature Link, and Science Direct. The literature search covered publications from 1998 to 2024, ensuring the inclusion of both foundational studies and the latest advancements. To maximize search efficiency and coverage, a combination of keywords was used: "NPSLE," "autoantibodies," "pathogenesis," "biomarker," "neuropsychiatric manifestations," "BBB," and "choroid plexus," as well as Boolean operators and truncations to account for variations in terminology.

Studies were selected based on predefined inclusion and exclusion criteria to ensure relevance and quality. *The inclusion criteria were*: original research articles, systematic reviews, meta-analyses, and clinical trials; studies explicitly addressing the role of antibodies in NPSLE pathogenesis, their potential as diagnostic or prognostic biomarkers, and their involvement in the disruption of the BBB and the BCB; publications in English that provided detailed methodology and specific data relevant to the research objective. *Exclusion criteria included*: studies lacking explicit data on antibodies or their role in NPSLE; case reports and editorials, as they were less likely to provide comprehensive or generalizable insights; studies focusing solely on lupus nephritis, cutaneous lupus, or other non-neuropsychiatric manifestations of systemic lupus erythematosus.

Data extraction and analysis. Data was systematically extracted using a structured template, focusing on study design, population characteristics, antibody roles in NPSLE pathogenesis, and their diagnostic or prognostic utility. Studies employing advanced techniques like immunohistochemistry, cytokine profiling, and neuroimaging received particular attention for their insights into antibody-CNS interactions. Each study was critically assessed for methodological rigor and relevance. The extracted data were synthesized narratively, emphasizing the heterogeneity in antibody profiles, their mechanistic roles in NPSLE, and their clinical implications. Trends and gaps in the literature were identified, highlighting areas requiring further research. Where available, quantitative data were incorporated to provide context for the significance of findings, such as correlations between antibody titers and clinical outcomes or imaging abnormalities.

Ethical considerations. Given the nature of the study as a review of existing literature, ethical approval was not required.

Limitations. This review is limited by its reliance on published literature in English, which may have excluded relevant studies available in other languages. Nonetheless, the comprehensive search strategy and the critical appraisal of the included studies provide a solid foundation for understanding the antibody-mediated mechanisms in NPSLE.

Results

Pathogenetic mechanisms of NPSLE

According to recent perspectives, NPSLE is a multifactorial process involving numerous pathogenetic pathways, ranging from the integrity of the BBB to the interaction of the immune cells with the brain tissue [7, 8]. Some scholars consider the integrity of the neuroimmune interfaces to be one of the key elements in NPSLE pathogenesis, which consist of the meningeal barrier, glymphatic circulatory system, BBB, and blood-CSF barrier (choroid plexus; BCB), neuroinflammation and interaction of brain tissue with different cytokines, autoantibodies and immune complexes, cerebrovascular lesions and direct interactions between central and peripheral nervous system cells (microglia activation, abnormal endothelial-immune cell interactions) [6]. However, there is no consensus on the activation and progression of this cascade of changes.

It is known that during the homeostatic state, the BBB, composed of specialized endothelial vessels surrounded by pericytes, astrocytic end-feet, and microglial cells, represents a very selective and robust barrier that limits the entry of several types of immune cells or inflammatory molecules into the brain parenchyma. The endothelial cells (EC), that reassemble the blood vessel wall, maintain robust tight junctions that effectively seal

the intercellular spaces and are characterized by diminished transcytosis, which is a consequence of a very specific set of transporters (GLUT1, MCT1, L1, γ^+, EAAT etc.) that regulates the entry and the afflux of different types of molecules and ions, what is very important, according to some authors, for the progression of immune reactions [5, 8]. The BCB operates using quite the same architectonics, the capillaries that form choroid plexus have fenestrations, but also serve as an educational gateway, allowing memory T cells to access and perform immunosurveillance on antigens and pathogens drained from the CSF [7, 8]. Conforming to specialized literature, the alteration in the permeability of the BBB and the BCB are one of the key parts of the neuroinflammatory process and the pathogenesis of the neuropsychiatric manifestations of NPSLE [5, 9]. Furthermore, as some authors suggest, due to the hyperactivity of both innate and adaptive immune systems, the homeostatic mechanisms of regulatory systems become impaired, and different immunological mechanisms and systems such as cytokine formation, the complement system, and autoreactivity from the immune cells for self-antigens start to modulate the permeability of the BBB [2, 4, 8]. The cytokines formed in vast quantities, such as tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and fibroblast growth factor-inducible 14 (Fn14) when bonded together induce the formation of different pro-inflammatory molecules such as IL-6, IL-8 and INCAM-1 (Intracellular adhesion molecule-1) in astrocytes [9]. Due to the large secretion of these substances, the production of tight junction proteins (occludin-5, JAM-A, ZO-1, etc.) is diminished, but the expression of such proteins as matrix metalloproteinases (MMPs) (MMP2, MMP9) is elevated in ECs, astrocytes, microglial cells, monocytes and macrophages, therefore disturbing the BBB permeability and its function, and allowing transmigration of inflammatory cells into the CNS parenchyma [7, 10]. Some studies have been published indicating that, in addition to the above-mentioned molecules, in large concentrations were found inflammatory cytokines like B-cell activating factor (BAAF), interferon-γ (IFN-γ), and interferon-α (IFN-α) [8, 11]. The concentration of these inflammatory cytokines is independent of their serum value, indicating that the hyperproduction site of these molecules occurs in the CNS [6]. Recent studies show that there is a very strong correlation between the serum concentration of IL-6 and NPSLE manifested with acute confusion states, the authors, Hirohata et al. 2021 stating that serum IL-6 concentration can be used as a biomarker for the severity of the NPSLE, the damage of the BBB being measured using the cerebrospinal fluid/serum albumin quotient (Qalb) [11]. Another route through which cytokines, autoantibodies, and immune cells can reach the brain tissue is the choroid plexus. In their study, Gelb et al. showed that sometimes the BBB can remain intact, and the gate through which the neuroinflammation starts is the dysfunctional choroid plexus, mainly its EC. Using the immunofluorescence technique, they showed that in some epithelial cells, the transcytosis process from the choroid plexus was elevated, leading to increased deposition of antibodies into the central nervous system at the choroid plexus and infiltration of lymphocytes through transepithelial migration creating a tertiary lymphoid structure [12, 13].

There is growing evidence that CNS cells are also influenced by all these inflammatory disturbances and play a key role in the pathogenesis of the NPSLE manifestations [7, 10, 11]. Microglial cells, which are long-lived resident macrophages, are classified into two types of population, M1 which is involved in the production of the proinflammatory cytokines, reactive oxygen species, and nitric oxide, and M2, with an inhibitory effect over the inflammatory processes. In the case of NPSLE, it is thought that the M1 polarized microglial cells are more active, a phenomenon called microgliolisis, leading to increased phagocytic activity and an intensified reactive state. Also, these cells exhibit functional alterations, such as increased internalization of synaptic materials leading to synapse loss [14, 15]. In mouse models, scientists identified microglial cells with a distinct transcriptional profile, termed "NP-SLE signature". These macrophages had downregulated or depleted genes that control the negative regulation of cytokine production, a positive regulator of cell motility, cell-cell adhesion, regulation of neurogenesis, angiogenesis, and upregulated and enriched with genes that control antigen processing and presentation of exogenous peptide antigen, immune effector process, complement activation of interferon-beta, positive regulation of macrophage activation and others [16].

Antibodies in NPSLE: types and their pathogenetic roles

One of the key features in the pathogenesis of SLE is the production of autoantibodies. According to the literature, approximately 116 antibodies have been reported, but none of them have been described fully from the pathogenetically point of view, their association remains controversial. As suggested by some researchers, from all this antibody pool, at least 11 brain-specific (anti-neuronal antibodies (Abs), brain-reactive Abs (BRAA), Anti-N-methyl-D-aspartate receptor Abs (NMDA), anti-microtubule-associated protein 2 Abs (MAP-2), anti-neurofilament Abs (ANFA), anti-synaptosomal Abs, anti-triosephosphate isomerase (TPI) Abs, anti-glial fibrillary acidic protein (GFAP) Abs, and anti-serum-lymphocytotoxic Abs (LCA)) and 9 systemic antibodies (anti-phospholipid (aPL)/cardiolipin (aCL) Abs, lupus anticoagulant (LAC), anti-beta 2- glycoprotein I (2GPI) Abs, anti-ribosomal P Abs (anti-P), anti-Ro Abs, anti-Sm Abs, anti-endothelial Abs (AECA), anti-serine proteinase (anti-PR3/C-ANCA) Abs, and anti-Nedd5 Abs) have been associated with NPSLE [2, 17]. Importantly, as highlighted by some researchers, the diversity and specificity of these antibodies suggest they play a multifaceted role in the pathogenesis of neuropsychiatric lupus, although their exact mechanisms remain to be fully elucidated.

Anti-N-methyl-D-aspartate Receptor (NMDAR) antibodies

The Anti-N-methyl-D-aspartate Receptor (NMDAR) is an ionotropic receptor, which modulates the function of a non-selective transmembrane ion channel (especially calcium entry into the cell). There are many subtypes of NMDA receptors, but all they share a similar structure – 2 N1 subunits with either 2 N2 or 2 N3 subunits. The subtype with the most physiological relevance being the N1/N2 NMDAR. These receptors are implicated in processes like long-term potentiation, synaptic plasticity, and memory formation. Besides that, because NMDA receptors are distributed in different areas of the brain such as the amygdala, hippocampus, and basal ganglia, and expressed and formed in CNS cells like pyramidal neurons, astrocytes, glial cells and ECs, they are thought to play a major role in the pathogenesis of some of the NPSLE manifestations. Studies suggest that antibodies against the N2 subunit are observed in 25%-40% of patients with SLE and represent a subset of anti-double-stranded DNA antibodies [1, 2, 18, 19]. The mechanisms through which the clinical symptoms form vary, but here are some possible explanations. Yoshio *et al.* showed that cerebrovascular endothelial inflammation that might cause cognitive dysfunction and psychiatric diseases in patients with SLE might be produced by the binding of these antibodies and activation of the ECs from the CNS. These ECs, through activation of the NF-κB signaling pathway, start to produce cytokines (mainly IL-6 and IL-8) which were shown experimentally that their mean production was higher in SLE patients' cells than in the control group. Also, the concentration of inflammatory adhesion molecules such as ELAM-1, ICAM-1, and VCAM-1 also were high, with an increased rate of production [20]. Also, an interesting mechanism of neuronal dysfunction can be through the hyperactivation of mitogen-activated protein kinase (MAP-kinase) and increased phosphorylation of MAP-2. This aberrant activation of the neurons can be another pathogenetic mechanism for the psychiatric manifestations [21]. Another important criterion for CNS function impairments is the status of the BBB. Studies show that in mice with healthy and undamaged BBB, there is no presence of brain pathology or any damage, and if there is an affection of the barrier, these antibodies bounded preferentially to hippocampal pyramidal neurons, leading to apoptotic death and deficit cognitive performances in those mice accompanied with MRI changes (decreased hippocampal N-acetyl aspartate/Creatinine (NAA/Cr) ratio) [17, 22-25].

Anti-Microtubule Associated Protein 2 antibodies

Microtubule-associated protein 2 (MAP-2) is a highly specific cytoskeletal component predominantly expressed in neurons. Its primary function is to support the dynamic framework required for cellular migration and division, as well as to regulate and sustain cellular reshaping processes. MAP-2 plays a crucial role in intracellular trafficking, leveraging its scaffolding properties to recruit cytoskeleton-modifying proteins and signaling pathway components to specific subcellular sites. This function underscores its importance in maintaining neuronal structure and function. MAP-2 is considered a microtubule stabilizer, minimizing the frequency of depolymerization events during microtubule formation and assembling, promoting their growth. This protein is also responsible for process formation and for maintaining mature dendritic structure; errors in the MAP-2 expression lead to decreased dendritic length and microtubule density in hippocampal neurons [26]. Yamada *et al.* in their study measured CSF concentration of anti-MAP-2 antibodies in a group of NPSLE patients and a non-NPSLE control group [21]. They found that anti-MAP-2 antibodies were present in 33.3% of patients with NPSLE and absent in the control group. The most prevailed symptom in antibody-positive was an acute confusional state as an NPSLE manifestation. This data leads to the conclusion that these antibodies are specific for NPSLE patients and could be used as a useful future biomarker in the diagnosis of NPSLE. Also, they measured the concentrations of CSF markers such as IL-6 and anti-ribosomal P protein antibodies and correlated them with the anti-MAP-2 antibody results. The results were that high concentrations of both IL-6 and anti-ribosomal P protein were found in patients with CSF anti-MAP-2 antibodies. Again, they point out the importance of the permeability and state of the BBB, stating that in anti-MAP-2 positive patients, the BBB damage was more severe, and respectively the IL-6 and anti-ribosomal P protein antibody concentration titters were elevated in CSF. Other studies associate the presence of anti-MAP-2 antibodies with neurological manifestations such as seizures, chorea, psychosis, headache, sensory neuropathy, and schizophrenia with an association value of 77% [2, 17, 27].

Anti-Glyceraldehyde-3-Phospate Dehydrogenase antibodies

Anti-Glyceraldehyde-3-Phospate Dehydrogenase (GAPDH) is an NAD^+ and inorganic phosphorus-dependent enzyme that catalyzes the conversion of glyceraldehyde-3-phosphate to 1,3-biphosphoglycerate within the glycolytic pathway. Besides glycolytic function, scientists identified its function in such fundamental cellular processes such as interaction with mRNAs and influencing their stability and gene expression, prevents rapid telomere shortening, interacts with p22 protein to aid in the microtubule organization process, and has an important role in DNA replication and its repair process [28, 29]. According to the opinions of some researchers, a potential mechanism by which GAPDH may contribute to neuronal dysfunction and the manifestations of NPSLE involves the production of toxic byproducts, particularly methylglyoxal (MG) [14, 17, 22]. MG is a highly reactive α-ketoaldehyde capable of oxidizing proteins, lipids, and other cellular components, resulting in cytotoxic effects and cellular damage [30]. Anti-GAPDH antibodies have been found in 50% of NPSLE patients with schizophrenia and major depression. Studies show that serum levels of anti-GAPDH antibodies were positively correlated with intracranial pressure and increased incidence of cerebrovascular lesions. These patients also showed high SLICC-ACR scores, suggesting that NPSLE patients with high

concentration titers of anti-GAPDH autoantibodies were in a more active disease status. Further investigations are needed to find out more correlations and exact mechanisms of how these antibodies are affecting CNS, but for now, anti-GAPDH autoantibodies have a future potential to become a biomarker in the NPSLE diagnostic process [31, 32].

Anti-Ribosomal P Protein (Rib-P) antibodies

Anti-Rib-P antibodies are considered a relative specific markers for SLE, found also in high titters in CSF of NPSLE patients, with a very high specificity and a sensitivity value between those of the anti-Sm (18.7%) and anti-DNA (74.0%) antibodies [33, 34]. These antibodies considered to have a higher affinity for neurons located in the hippocampus, cingulate cortex, primary olfactory piriform cortex, and all parts of the limbic system. The primary target of these antibodies is the epitopes located in the C-terminal end of 3 highly conserved phosphoproteins P_0, P_1, and P_2, which are components of the 60S subunit of the ribosomes. Besides this target, in the CNS, anti-Rib-P antibodies cross-react with another high-mass plasma membrane protein called neuronal surface P antigen (NSPA). One of the roles of the NSPA is to enhance glutamatergic postsynaptic transmission in the hippocampal neurons, involving both AMPAR and NMDAR activation, playing a major role in long-term potentiation and memory tasks. Because of its relation to NMDAR, anti-Rib-P antibodies can reproduce or even enhance the neuronal effects of anti-NMDAR in SLE patients [35]. According to some researchers, a potential mechanism for how these antibodies induce neuropsychiatric manifestations can be due to their effect on calcium homeostasis [22, 25, 28]. Rats exposed to anti-Rib-P antibodies showed a very rapid and sustained increase in cytosolic calcium in neurons. This resulted in neuronal stress, which was characterized by reduced denditric, decreased viability, nuclear alterations, and activation of the apoptotic marker caspase-3 [36, 37]. High titers of these antibodies are associated with an active phase of the SLE, with the most characteristic neuropsychiatric manifestations being mood disorders, long-term depression-like symptoms, psychosis, seizure, coma, and deficits in attention and planning [35, 38].

Anti-Phospholipid (aPL) antibodies (anti-cardiolipin, lupus coagulant, anti-β2-glycoprotein)

Besides the autoimmunity impact on the nervous system and the interaction of the antibodies with specific neuronal targets, another important trigger that leads to NPSLE manifestations is the ischemic processes. A key component of ischemic injury is the antiphospholipid antibody syndrome (APS) and the presence of the aPL antibodies. These antibodies are directed against the plasma proteins, especially β_2-glycoprotein (β_2-GPL), though their name states otherwise. Following antibody binding, the affinity of β_2-GPL to anionic phospholipids is greatly increased, starting to compete for its interaction with clotting factors for these phospholipids. Another binding target of this aPL- β_2-GPL complexes are platelets, specifically the LRP-8 (an LDL receptor-related protein) which in consequence activates them and increases their adhesion to collagen and their aggregation, raising the risk of thrombosis, due to the hypercoagulable state. Another implication of these antibodies in the coagulation processes is the inhibition of the nitric oxide formation by the endothelial nitric oxide synthetase resulting in a diminished bioavailability [39-42]. One of the most common neuropsychiatric symptoms found in aPL-positive SLE patients were cerebral ischemia, placing these patients in the high-risk group. These recurrent ischemic events are one of the main causes of other neuropsychiatric manifestations such as dementia, cognitive dysfunction, depression, psychosis, and seizures [43, 44]. Also, studies suggest that there is a higher prevalence of aPL in NPSLE compared with SLE patients lacking neuropsychiatric manifestations [45].

Other antibodies

In SLE patients, including those with neuropsychiatric symptoms, among brain-specific antibodies also are identified antinuclear antibodies (ANA). These antibodies can interact with cellular self-antigens like their nucleus, ribonucleoproteins, histone proteins, double-stranded DNA (dsDNA), DNA-histone complexes, various nuclear enzymes, and other antigens. Even though they are found in about 90% of patients with SLE and NPSLE, their titers are considered nonspecific for diagnosis due to frequent false positives, and they show a low statistical association with NPSLE. In contrast, the situation is different for the extractable nuclear antigen (ENA) antibodies. These are a subset of ANAs, named for their extraction from the acid-soluble, non-histone fraction of the cell nuclei and are regarded as more sensitive markers. Besides those mentioned in the above paragraphs, antibodies such as anti-Ro anti-LA, anti-Sm, anti-dsDNA, and others are also associated with NPSLE, with patients being positive for these antibodies in 50-60% of cases. Some studies suggest that anti-Sm antibodies are associated with NPSLE pathogenesis and BBB disruption, leading to neuropsychiatric manifestations such as organic brain syndrome and acute confusional state. Another interesting marker that can help in NPSLE diagnosis are anti-ds-DNA antibodies. Their serum concentration is variable in time depending on the activity of the disease and are associated with poor performance of visuospatial skills, attention, and executive function. Even though there are studies that conclude that systemic autoantibodies can be used as a predictive and diagnostic tool, true for some, further investigations should be performed to discover their true role and explain the importance of all these antibodies in the SLE and NPSLE pathogenesis and symptom formation [1, 17, 46]. Summarizing the data from the specialized literature that we have analyzed, we propose a comprehensive integrative synthesis that provides a broad perspective on the clinical utility of autoantibodies in NPSLE, facilitating the optimization of diagnostic and therapeutic strategies (Table 2).

Table2. Clinical utility of autoantibodies in NPSLE.

Autoantibody	Pathogenetic mechanism	Clinical correlations	Diagnostic utility	Prognostic utility	Therapeutic implications
Anti-NMDAR	Neuronal damage through excessive NMDA receptor activation and neuronal apoptosis	Psychosis, cognitive impairment, seizures	Present in 25-40% of NPSLE patients, associated with severe neuropsychiatric involvement	Correlated with brain lesion severity and cognitive decline	High titers may indicate the need for aggressive immunosuppressive therapy (rituximab, corticosteroids)
Anti-MAP-2	Synaptic dysfunction and neuronal structural damage	Acute confusional state, seizures, schizophrenia	Highly specific for NPSLE, absent in SLE patients without neuropsychiatric involvement	High titers correlate with severe cognitive impairment and executive dysfunction	May indicate the need for biologic therapy and close monitoring of disease progression
Anti-Rib-P	Neuronal dysfunction through impaired ribosomal protein metabolism	Psychosis, severe depression, acute confusional state	Moderate sensitivity but high specificity for NPSLE	Associated with severe episodes of psychosis and depression, requiring close monitoring	High titers may indicate the need for intensified immunosuppressive therapy
Anti-GAPDH	Metabolic and oxidative neuronal damage via accumulation of toxic byproducts (methylglyoxal)	Major depression, schizophrenia, cerebrovascular lesions	Correlated with neurovascular damage, more common in severe NPSLE cases	Associated with rapid and progressive neurocognitive decline	Potential therapeutic target in combination with neuroprotective agents
aPL	Prothrombotic state induction via endothelial and coagulation pathway dysfunction	Stroke, vascular dementia, cerebral thrombosis	Essential for assessing thrombotic risk in NPSLE patients	Correlated with recurrent ischemic cerebral events	Requires chronic anticoagulation therapy (warfarin, heparin)
Anti-dsDNA	Immune complex formation and complement activation leading to endothelial damage	Cognitive impairment, neurovascular involvement, lupus encephalopathy	Correlates with overall disease activity but has low specificity for NPSLE	High titers indicate a risk of cerebral involvement and rapid disease progression	May guide the need for intensified immunosuppressive therapy (cyclophosphamide, belimumab)
Anti-ENA (Ro, La, Sm, U1-RNP)	Generalized immune dysfunction and autoimmune neuronal damage	Cognitive impairment, psychosis, peripheral sensory dysfunction	Useful for stratifying patients with NPSLE and severe SLE forms	Correlated with progressive neurological deterioration	May guide therapeutic decisions regarding the use of biologic agents

Note: *NPSLE - neuropsychiatric systemic lupus erythematosus, SLE - neuropsychiatric systemic lupus erythematosus, aPL – anti-phospholipid antibodies, anti-NMDAR – anti-N-methyl-D-aspartate receptor antibodies, anti-MAP-2 – anti-Microtubule-Associated Protein 2 antibodies, anti-Rib-P – anti-Ribosomal P protein antibodies, anti-GAPDH – anti-Glyceraldehyde-3-Phosphate Dehydrogenase antibodies, anti-phospholipid (aPL) – anti-phospholipid antibodies, including anti-cardiolipin (aCL), lupus anticoagulant (LAC), and anti-β2-glycoprotein I (β2-GPI) antibodies, anti-dsDNA – anti-double-stranded DNA antibodies, anti-ENA (Ro, La, Sm, U1-RNP) – anti-Extractable Nuclear Antigen antibodies, including anti-Ro (SSA), anti-La (SSB), anti-Smith (Sm), and anti-U1-ribonucleoprotein (U1-RNP) antibodies. The most diagnostically relevant autoantibodies are anti-NMDAR, anti-MAP-2, and anti-Rib-P, as they are strongly correlated with severe neuropsychiatric manifestations. aPL and anti-dsDNA are crucial for assessing vascular and ischemic risk in NPSLE patients. High autoantibody titers are correlated with disease severity, allowing patient stratification and personalized treatment approaches. The presence of specific autoantibodies can guide therapeutic decisions, including the use of corticosteroids, biologic agents (rituximab, belimumab), or anticoagulants, depending on the patient's risk profile.*

Discussions

This study critically examines the current understanding of NPSLE, focusing on its pathogenesis and the role of autoantibodies in clinical manifestations. Despite considerable progress, NPSLE remains a complex condition with significant diagnostic and therapeutic challenges. Numerous autoantibodies have been identified in association with NPSLE, providing insights into its pathogenesis. However, an ideal diagnostic tool has yet to be identified, negatively affecting the management of such patients and NPSLE remaining "a disease complex much in search of pathogenetic autoantibodies, whereas most of the antibodies thus far described in NPSLE are still in search of a disease" [47]. This limitation has led to the characterization of NPSLE as a condition where the identified antibodies often lack clear and consistent associations with the disease, complicating clinical decision-making and patient management.

The discovery of brain-specific autoantibodies such as anti-NMDAR, anti-MAP2, and anti-Rib-P has offered important insights into NPSLE pathogenesis. These antibodies have been associated with distinct neuropsychiatric manifestations, such as depression and cognitive dysfunction linked to anti-NMDAR, and seizures and psychosis associated with anti-MAP2 [21, 27, 29, 35]. Anti-Rib-P antibodies show strong correlations with severe depression and psychosis [17, 21, 34]. Despite these associations, inconsistencies in their specificity and sensitivity reduce their reliability as standalone diagnostic markers [11, 22, 41]. Future research should aim to identify combinations of these biomarkers to improve diagnostic accuracy and their correlation with specific clinical manifestations.

The integrity of the BBB emerges as a critical factor in the development of NPSLE. Disruption of the BBB facilitates the entry of inflammatory and neurotoxic mediators into the CNS, exacerbating neuronal damage. Understand-

ing how autoantibodies, cytokines, and other pathological mechanisms interact with the BBB remains a key research priority. Current studies emphasize the importance of developing assays to detect early BBB dysfunction, which could serve as predictive markers for disease progression and improve early intervention strategies [17, 25, 32].

A major challenge in advancing NPSLE research is the lack of standardized diagnostic criteria. Variations in patient selection, antibody testing methodologies, and result interpretation have led to inconsistent findings across studies [7, 9, 16, 28]. This lack of standardization hampers the ability to draw definitive conclusions about the role of autoantibodies in NPSLE. Efforts to establish unified criteria for patient inclusion, standardized assays for antibody detection, and consistent protocols for measuring antibody dynamics over time are essential. Integrating modern diagnostic tools such as advanced neuroimaging and CSF analysis will further enhance the understanding of NPSLE and refine diagnostic approaches [34, 37, 40].

Contradictory findings in the literature regarding the utility of autoantibodies as biomarkers highlight the need for more robust research. While some studies suggest strong correlations between specific autoantibodies and neuropsychiatric symptoms, others fail to confirm these relationships [25, 41, 43]. We tried to rank the most relevant biomarkers in NPSLE according to their specificity for the disease and clinical applicability (Table 3), considering their role in diagnosis, prognosis, and treatment guidance [22-27, 35, 39, 41, 43]. But a lot of inconsistencies may arise from differences in study design, population heterogeneity, or methodological limitations. Future investigations should prioritize multicenter studies with larger, diverse cohorts and longitudinal designs to validate these associations and establish clearer connections between antibody titers, disease activity, and clinical outcomes.

Table 3. Ranking of biomarkers in NPSLE based on specificity and clinical utility.

Biomarker	Specificity for NPSLE	Diagnostic utility	Prognostic utility	Clinical applicability
Anti-NMDAR	⋆ ⋆ ⋆ ⋆	Highly specific for NPSLE; associated with psychosis, seizures, cognitive dysfunction	Correlates with cognitive impairment severity and brain lesion extent	Guides aggressive immunosuppressive therapy (rituximab, corticosteroids)
Anti-MAP-2	⋆ ⋆ ⋆ ⋆	Found almost exclusively in NPSLE patients; linked to acute confusional states	High titers correlate with severe cognitive dysfunction and executive impairment	Helps identify high-risk patients who need close neurological monitoring
Anti-Rib-P	⋆ ⋆ ⋆ ⋆	Moderate sensitivity, high specificity for NPSLE; strongly linked to psychosis and depression	Associated with worsening neuropsychiatric symptoms	Can predict need for early immunosuppressive therapy intensification
aPL	⋆ ⋆ ⋆	Important for identifying vascular complications (stroke, dementia)	High titers predict recurrent ischemic cerebral events	Guides long-term anticoagulation (warfarin, heparin) and risk stratification
Anti-GAPDH	⋆ ⋆ ⋆	Correlates with major depression and schizophrenia in NPSLE	Predicts neurovascular damage and progressive cognitive decline	Potential therapeutic target for neuroprotective agents
Anti-dsDNA	⋆ ⋆	Indicates general SLE disease activity but has low specificity for NPSLE	Correlated with CNS involvement and disease progression	Supports broader SLE management rather than NPSLE-specific treatment
Anti-ENA (Ro, La, Sm, U1-RNP)	⋆ ⋆	Useful for identifying severe SLE patients with neuropsychiatric involvement	Associated with progressive neurological deterioration	May inform decisions on biologic therapy (belimumab, rituximab)

Note: *NPSLE – neuropsychiatric systemic lupus erythematosus, SLE – neuropsychiatric systemic lupus erythematosus, CNS – central nervous system, aPL – anti-phospholipid antibodies, anti-NMDAR – anti-N-methyl-D-aspartate receptor antibodies, anti-MAP-2 – anti-Microtubule-Associated Protein 2 antibodies, anti-Rib-P – anti-Ribosomal P protein antibodies, anti-GAPDH – anti-Glyceraldehyde-3-Phosphate Dehydrogenase antibodies, anti-phospholipid (aPL) – anti-phospholipid antibodies, including anti-cardiolipin (aCL), lupus anticoagulant (LAC), and anti-β2-glycoprotein I (β2-GPI) antibodies, anti-dsDNA – anti-double-stranded DNA antibodies, anti-ENA (Ro, La, Sm, U1-RNP) – anti-Extractable Nuclear Antigen antibodies, including anti-Ro (SSA), anti-La (SSB), anti-Smith (Sm), and anti-U1-ribonucleoprotein (U1-RNP) antibodies. Anti-NMDAR, Anti-MAP-2, and Anti-Rib-P are the most specific biomarkers for diagnosing NPSLE and correlating with severe neuropsychiatric manifestations. aPL and anti-GAPDH are important for predicting vascular and metabolic complications that contribute to neurological decline. Anti-dsDNA and Anti-ENA are less specific but still useful in broader disease stratification for SLE patients. Biomarker-based stratification can guide personalized treatment decisions, optimizing immunosuppressive and anticoagulation therapy to prevent complications.*

Given the complexity of NPSLE, a personalized approach to patient management is crucial [32, 39, 45, 47]. Advances in biomarker research, imaging techniques, and CSF analysis hold promise for tailoring diagnostic and therapeutic strategies to individual patients. Collaborative efforts among rheumatologists, neurologists, and immunologists are necessary to develop comprehensive care protocols [15, 21, 39, 47]. The ultimate goal is to establish precise, biomarker-driven approaches that address the systemic and neuropsychiatric manifestations of lupus, improving patient outcomes and quality of life.

While significant progress has been made in understanding NPSLE, many questions remain unanswered. The interplay between autoantibodies, BBB dysfunction, and neuroinflammation is a critical area of ongoing research. Addressing these gaps through interdisciplinary collabora-

tion and innovative methodologies will be essential for advancing the diagnosis, prognosis, and management of this multifaceted condition.

Conclusions

NPSLE represents a complex and multifaceted condition that challenges clinicians and researchers alike due to its diverse clinical manifestations, intricate pathogenesis, and diagnostic uncertainties. Despite significant advances in understanding the role of autoantibodies and the critical influence of blood-brain barrier (BBB) integrity, an ideal diagnostic tool remains elusive. Autoantibodies, such as anti-NMDAR, anti-MAP2, and anti-Rib-P, offer valuable insights into disease mechanisms, correlating with specific neuropsychiatric symptoms. However, inconsistencies in sensitivity, specificity, and clinical utility highlight the need for more precise biomarkers.

The disruption of neuroimmune interfaces, particularly the BBB and the blood-cerebrospinal fluid barrier (BCB), is central to the pathogenesis of NPSLE. These disruptions allow pathogenic autoantibodies and inflammatory mediators to penetrate the central nervous system (CNS), amplifying neuroinflammatory processes. Understanding the molecular interplay between these barriers, cytokines, and autoantibodies is crucial for identifying early markers of disease progression and tailoring interventions.

Standardization in diagnostic criteria, antibody detection assays, and patient selection are urgently required to resolve discrepancies in current literature and improve research outcomes. Modern neuroimaging techniques and cerebrospinal fluid analysis offer promising avenues for enhancing diagnostic accuracy and understanding disease mechanisms.

A personalized approach to patient management, integrating biomarker-driven diagnostics and therapeutic strategies, holds promise for improving outcomes in NPSLE. Collaborative efforts between rheumatologists, neurologists, and immunologists are essential to develop comprehensive care protocols and advance precision medicine in this field.

Despite substantial progress, significant gaps remain in our understanding of NPSLE. Addressing these challenges through interdisciplinary research, innovative methodologies, and standardized protocols will pave the way for more effective diagnosis and management of this enigmatic condition, ultimately improving patient care and quality of life.

Competing interests

None declared.

Contribution of authors

ER and CN conceived the research idea; CN, ER, LG developed the aim and objectives of the literature review; CN, AP, MS, IL drafted the manuscript and realized the literature search; ER, LG and LC designed the study and revised the manuscript critically. All authors have read and approved the final version of the manuscript.

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REVIEW ARTICLES

Chronic kidney disease – a major public health problem

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ABSTRACT

Introduction. Chronic kidney disease (CKD) is a major and growing global public health problem, contributing to significant morbidity, mortality, and financial strain on healthcare systems. Despite available preventive measures, CKD often remains underdiagnosed and insufficiently addressed by health policies worldwide.

Materials and methods. A literature review was conducted using the MEDLINE electronic database via PubMed, Scopus, and the HINARI (Research4Life) program, focusing on studies published since 2001. Search terms included "primary care", "chronic kidney disease", "chronic kidney disease public health", and "chronic kidney disease costs". Original articles, meta-analyses, and systematic reviews were included, with English-language articles prioritized. Bibliographic references of selected publications were also examined to identify additional relevant studies.

Results. CKD affects approximately 700-850 million people globally, with rising prevalence and mortality rates, especially in low- and middle-income countries. The disease disproportionately burdens vulnerable populations and health systems due to high direct and indirect costs, particularly for advanced-stage care. While cost-effective prevention and early detection strategies are available, their implementation is uneven, and policy responses have historically lagged. Successful national initiatives demonstrate that early intervention and integrated care can reduce the incidence and economic impact of end-stage kidney disease.

Conclusions. CKD is a preventable, yet increasingly prevalent disease that requires urgent public health action. Prioritizing early detection, integrated care models, and policy reforms can significantly curb its global burden. Coordinated efforts at international, national, and local levels are essential to translate existing knowledge into effective practice and reduce the societal and financial costs of CKD.

Keywords: chronic kidney disease, global health, prevention, early detection, health policy, economic burden, integrated care, public health.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

The optimal strategies for global implementation of early CKD detection and prevention remain inadequately defined.

The research hypothesis

Strengthening early detection and prevention policies can reduce CKD burden and associated healthcare costs globally.

The novelty added by the manuscript to the already published scientific literature

It synthesizes global CKD burden data with policy gaps, highlighting cost-effective interventions and successful country models. It synthesizes global CKD burden data with policy gaps, highlighting cost-effective interventions and successful country model.

Introduction

Chronic kidney disease (CKD) is a progressive loss of kidney function over months to years, often culminating in end-stage kidney disease that requires dialysis or transplantation. It is typically defined by a sustained reduction in glomerular filtration rate (GFR <60 mL/min/1.73 m^2) or markers of kidney damage (e.g. proteinuria) persisting for at least 3 months [1]. CKD is usually asymptomatic in early stages, and many patients remain undiagnosed until significant loss of kidney function has occurred. This insidious course, combined with its widespread prevalence and severe outcomes, has established CKD as a major public health concern. An issue qualifies as a public health problem when it imposes a large and growing disease burden (mortality, morbidity, reduced quality of life, and high costs), disproportionately affects vulnerable populations, and lacks fully effective preventive strategies. CKD meets all of these criteria: it is common and increasing worldwide, leads to substantial premature mortality and disability, incurs enormous healthcare costs, and yet remains under-recognized and insufficiently addressed by health systems [2]. In this article, we review the global burden of CKD, the financial and societal impact of the disease, and current health policy responses and initiatives aimed at CKD prevention and management. We also discuss the need for strengthened policies and health system reforms to curb the growing CKD epidemic.

Material and methods

A search of scientific papers published since 2001 in the MEDLINE electronic database was performed using the search engine PubMed, Scopus and HINARI (Health InterNetwork Access to Research Initiative) – Research4Life program, selecting full-text articles provided by these platforms. The search terms used (in English) were: „primary care", „chronic kidney disease", „chronic kidney disease public health", "chronic kidney disease costs". Original articles, meta-analyses and systematic reviews were selected. No language limits were set, but articles in English were prioritized. Additionally, the bibliography of the selected articles was studied, in order to find other articles relevant to this topic.

Results and discussion

Global Burden of CKD. Prevalence and trends

CKD affects an estimated 700-850 million people worldwide, roughly 9-10% of the global population [1]. Global prevalence has risen significantly over the past decades, in part due to population aging and the growing prevalence of risk factors such as diabetes, hypertension, and obesity. Between 1990 and 2017, the all-age prevalence of CKD increased by about 29% [1]. By 2017 there were approximately 697 million cases of CKD (stages 1-5) globally, and recent estimates put the number of people with kidney diseases (including earlier-stage CKD) as high as 850 million. Prevalence is strongly age-dependent – CKD is present in over one-third of individuals above 65 years old in some regions [3, 4]; and is often higher in women than men, although severity tends to be greater in men. Notably, the burden of CKD is distributed unevenly across the world. Over two-thirds of the global CKD cases are in low- and middle-income countries (LMICs) [5], where access to early diagnosis and treatment is limited. As a result, the vast majority of people living with CKD in resource-poor settings are unaware of their condition [5]. Studies indicate that as many as 9 in 10 individuals with CKD in low-resource environments remain undiagnosed and untreated [5]. This under-diagnosis leads to a silent progression of disease in the population and reflects a major gap in healthcare delivery.

Mortality and outcomes

The consequences of CKD in terms of mortality and morbidity are severe. Global deaths attributable to CKD have been rising steadily. In 2017, an estimated 1.2 million people died from CKD complications worldwide [1]. By 2021, annual CKD deaths reached approximately 1.5 million. Unlike many other major non-communicable diseases (NCDs) which have seen improvements, CKD is unique in that its age-adjusted mortality continues to increase. It is currently the only major NCD with a rising mortality rate globally [5]. Over the past two decades, CKD climbed from the 17th to the 10th leading cause of death worldwide, and it is now recognized as the third fastest-growing cause of death [5]. Projections are alarming – by 2040, CKD is expected to rank as the 5th leading cause of years of life lost globally, reflecting both high mortality and the younger age at which some CKD deaths occur. The burden of CKD is also magnified by its strong link to cardiovascular disease. Patients with CKD have a markedly elevated risk of cardiovascular morbidity and mortality; CKD acts as a "risk multiplier" in individuals with hypertension or diabetes [1]. Most CKD patients are far more likely to die of cardiovascular causes (such as heart attacks or strokes) before ever progressing to end-stage renal disease. In fact, even mild to moderate reductions in kidney function are associated with heightened risks of all-cause and cardiovascular death. CKD also significantly worsens quality of life due to symptoms like fatigue, anemia, bone and mineral disorders, and depression in advanced stages [6]. Thus, the global burden of CKD encompasses not only those who reach kidney failure, but also millions who suffer disability or die prematurely from CKD and its complications.

Disparities and regional patterns

There are pronounced disparities in CKD outcomes both between and within countries. Economically disadvantaged populations and ethnic minorities often face higher CKD incidence and worse outcomes, reflecting the interplay of risk factors and access to care [2]. For example, indigenous communities and African-ancestry populations in various countries experience higher rates of CKD progression and end-stage renal disease, partly due to higher burden of diabetes/hypertension and reduced access to preventive care. Globally, patients in low-income countries frequently present with more advanced CKD or kidney failure and have limited access to life-saving renal replacement therapy. It is estimated that millions of people develop kidney failure every

year but die without receiving dialysis or transplant, due to lack of access [5]. Even in high-income countries, about 15-20% of patients initiating dialysis die within one. In poorer regions, outcomes are far worse: "millions more" who need dialysis or transplant are simply unable to obtain it and succumb prematurely. Virtually all of these untreated kidney failure deaths occur in low- and lower-middle-income countries. These grim statistics highlight CKD as a global health emergency that has not yet received commensurate policy attention. While international targets for reducing NCD deaths focus on cardiovascular disease, cancer, diabetes, and chronic lung disease, CKD has historically been neglected in global health strategies [2, 5]. The rising prevalence and mortality of CKD, and its disproportionate impact on vulnerable populations, clearly underscore the need for urgent public health action.

Financial and societal burden of CKD

Beyond its health toll, CKD imposes an enormous economic and societal burden on patients, healthcare systems, and societies at large. Direct healthcare costs associated with CKD are substantial at all stages and skyrocket for patients who progress to kidney failure. Management of early-stage CKD (with medications, monitoring, and treating comorbidities) is relatively cost-effective, but once patients require dialysis or transplantation – collectively known as kidney replacement therapy (KRT) – the expenses are among the highest in medicine. Annual treatment costs per patient on dialysis often range from US$50,000 to $100,000 in high-income countries [7], far exceeding the costs in earlier CKD stages (by a factor of nearly 20 in some estimates). Even transplantation, which is more cost-effective in the long run, involves high upfront costs (approximately $75,000 in the first year, and ~$17,000 per year thereafter for immunosuppression and follow-up) [7]. These per-patient costs translate into a massive aggregate burden.

At the health system level, CKD and kidney failure care consume a disproportionately large share of resources. For example, in the United States, people with kidney failure constitute <1% of Medicare beneficiaries but account for over 6% of total Medicare spending [8, 9]. In 2021, Medicare spending on CKD patients aged ≥65 was $76.8 billion, which represented one quarter of all Medicare expenditures for that age group [1]. This illustrates how expensive CKD care can be, even in a wealthy country. The costs are rising as CKD prevalence grows – in the U.S., Medicare costs for CKD increased by 40% between 2011 and 2021. Other countries face similar challenges: in China, the annual economic burden of CKD is projected to climb from $179 billion in 2019 to $198 billion by 2025 [1]. A recent multi-country analysis of 31 nations (across Americas, Europe, Middle East, and Asia-Pacific) found that direct costs of diagnosed CKD and KRT will increase by about 9.3% from 2022 to 2027, reaching an estimated $407 billion across these countries [10]. By 2027, CKD is expected to consume an average of 6.4% of total health expenditures in those countries, up from 5.6% in 2022 [10]. This rising cost trajectory is unsustainable for many health systems. Particularly striking is the concentration of costs in advanced CKD: although patients receiving dialysis or transplant will comprise only ~5% of all diagnosed CKD cases in 2027, they are projected to account for nearly 46% of total CKD-related healthcare costs [10]. This imbalance highlights that late-stage CKD care (dialysis and transplant) is extremely costly, and that strategies focusing on earlier intervention could yield major cost savings.

Indirect costs and societal impact

CKD's burden extends beyond direct medical spending. There are substantial indirect costs due to lost productivity, as CKD often affects people in middle age and can lead to reduced work capacity, long-term disability, or premature death during prime working years. Patients with advanced CKD and those on dialysis commonly cannot maintain full employment due to the illness and time requirements of treatment. In addition, CKD patients frequently experience impaired quality of life, fatigue, and cognitive effects that reduce productivity even if they remain employed. A recent analysis in Australia estimated that over a 10-year period, CKD (including end-stage disease) would cause a cumulative productivity loss equivalent to US$91 billion in lost gross domestic product [11]. Notably, nearly half of this economic loss was attributed to reduced on-the-job productivity among individuals with early-stage CKD, and another 20% was due to premature exit from the workforce in later-stage CKD [11]. This example underlines that even early/moderate CKD can inflict a broad economic drag via subtle declines in worker performance and health. On a household level, CKD often results in catastrophic expenditures for families, especially in countries lacking universal health coverage. The cost of dialysis can impoverish patients and their families; many resort to selling assets or forgoing treatment. In low-resource settings, the majority of patients who develop kidney failure will die for lack of affordable treatment, as dialysis is either unavailable or prohibitively expensive without government support [5]. Globally, it is estimated that at least 2.3 million people die each year because they cannot access dialysis or transplantation in time [5] – a stark illustration of the societal cost in lives lost due to resource constraints. Furthermore, CKD creates psychosocial burdens: patients often suffer from depression, dependence on caregivers, and reduced ability to participate in family and community life. Taken together, the financial burden (direct and indirect) and the human burden of CKD are enormous. In recognition of these impacts, the World Health Organization (WHO) now classifies CKD as a major global health concern and includes it in global burden of disease assessments [1], though policy responses have lagged behind the magnitude of the problem.

Prevention and early detection strategies

Given the high costs and poor outcomes associated with advanced CKD, there is a strong imperative to shift focus toward prevention, early detection, and slowing disease progression. The majority of CKD cases develop on a background of known risk factors – principally type 2 diabetes mellitus, hypertension, and to a lesser extent glomerulonephritis, obesity, and aging-related decline in kidney func-

tion. In high-income settings, roughly 1 in 3 adults with diabetes and 1 in 5 adults with hypertension have CKD [5]. These facts underscore that effective prevention of CKD is largely entwined with control of its upstream drivers. Primary prevention involves reducing the incidence of CKD by aggressive management of risk factors in the general population. Public health measures to combat obesity, promote healthy diets (salt and protein moderation), reduce tobacco use, and encourage physical activity can in turn lower the population prevalence of hypertension and diabetes, yielding long-term reductions in CKD incidence [12]. Many of these interventions (e.g. salt reduction campaigns, sugar taxes, smoking cessation programs) are cost-effective from a societal perspective and have co-benefits for other NCDs [13]. In addition, improving social determinants – such as reducing poverty and expanding access to basic healthcare – is important, as CKD disproportionately afflicts disadvantaged groups and those with limited healthcare access [2]. Environmental factors are also receiving attention; for example, recurring severe dehydration and heat stress in manual laborers (exacerbated by climate change) have been linked to a form of CKD of unknown origin in certain regions [1]. Addressing such occupational and environmental risks (through ensuring access to hydration, shade, etc.) is an emerging component of CKD prevention in affected areas.

Early detection and secondary prevention

Detecting CKD early – before significant loss of kidney function – allows for interventions that can slow or halt progression to end-stage kidney disease. Key measures include optimal control of blood pressure, strict glycemic control in diabetics, use of renal-protective medications, and avoidance of nephrotoxic drugs. For instance, use of renin-angiotensin system blockers (ACE inhibitors or ARBs) in proteinuric CKD is a well-established strategy to reduce progression risk. In recent years, new classes of medications (such as SGLT2 inhibitors and non-steroidal mineralocorticoid antagonists like finerenone) have demonstrated the ability to further slow CKD progression in patients with diabetes and other high-risk groups, on top of standard care [14]. These therapies, alongside optimized management of comorbid cardiovascular conditions, can significantly improve outcomes – but only if patients are identified early in the disease course. Unfortunately, as noted, most CKD cases remain undiagnosed until late stages in many settings. Improving early detection is therefore a public health priority.

The most practical approach is targeted screening for CKD in high-risk populations rather than universal screening. Routine testing for kidney disease (e.g. measuring serum creatinine to estimate GFR, and urine albumin levels) is recommended for individuals with diabetes, hypertension, cardiovascular disease, or a family history of kidney disease. Guidelines also advise screening older adults and certain ethnic minorities who have elevated risk [15, 16]. Studies have shown that focused screening of high-risk groups is cost-effective and can lead to early interventions that delay CKD progression. In contrast, indiscriminate population-wide screening is not cost-effective, given the low yield in low-risk people and the costs of widespread testing. Thus, healthcare systems should embed CKD screening into chronic disease management programs – for example, ensuring every diabetic or hypertensive patient in primary care is periodically evaluated for kidney function. Simple tests like estimated GFR and urine albumin-creatinine ratio suffice to detect early CKD. The challenge, however, is implementation: in many low-income countries, even these basic tests are not readily available. A global survey found that among low-income countries, only about one-third could measure serum creatinine at primary care level, and none had capacity for routine urine albumin testing [2]. Even in some high-income countries, significant gaps exist in primary care testing for CKD (with only ~60% of practices reporting ability to measure albuminuria) [2]. Closing these gaps is an important task for health systems – investing in laboratory capacity and training so that CKD can be identified early, particularly in high-risk patients.

Lifestyle and risk factor management

When early-stage CKD or CKD risk factors are identified, aggressive management can substantially improve outcomes. Blood pressure control is paramount. Studies suggest that maintaining blood pressure <130/80 mmHg in CKD patients (especially with proteinuria) slows kidney damage progression. Tight glycemic control in diabetics (targeting individualized HbA1c goals) similarly reduces the development of diabetic nephropathy [17]. Other measures include managing dyslipidemia, encouraging weight loss in obese patients, avoiding NSAIDs and other nephrotoxins, and ensuring adequate hydration in those at risk of recurrent volume depletion. Patient education is also critical – people with early CKD should be counseled on dietary modifications (e.g. moderate protein intake, low salt, avoiding high-phosphate processed foods) and the importance of medication adherence. Multidisciplinary care (involving dietitians, pharmacists, and nurses) has proven beneficial in CKD management programs [18]. In countries like Taiwan, a concerted effort to implement CKD care programs has yielded impressive results. Taiwan's National Health Insurance launched a nationwide CKD prevention program with pay-for-performance incentives for providers starting in 2006, coupled with patient education on pre-dialysis care. This comprehensive approach – involving early referral to nephrologists, dietitian counseling, and tightly managing risk factors – has significantly lowered the incidence of end-stage kidney disease in Taiwan [18]. Analyses show that after these programs began, the long-term trend in dialysis initiation in Taiwan shifted downward, with a net reduction of about 1% per year in new kidney failure cases [18]. This example demonstrates that early intervention strategies can translate into fewer patients needing costly dialysis, validating the importance of prevention in national policy.

Health policy responses and initiatives

Addressing CKD as a public health crisis requires coordinated action at multiple levels: international organizations, national governments, and local health systems all have roles to play. To date, however, CKD has not received the

same level of policy priority as other major NCDs, and this gap is only beginning to be rectified [2]. Below, we outline the current landscape of health policy responses and ongoing initiatives aimed at CKD prevention and management, as well as needed reforms.

International and WHO initiatives

The global health community has started acknowledging CKD's importance. The World Health Organization has included CKD in its Global Burden of Disease assessments and in 2020 added "kidney diseases" to the top 10 causes of death list (ranked 10th worldwide) [5], raising awareness among policymakers. However, CKD is still not explicitly listed alongside the "big five" NCDs (cardiovascular disease, cancer, diabetes, chronic respiratory disease, and stroke) in many WHO strategic documents. This historical omission at the highest policy level has trickled down – many countries' national NCD plans omit kidney disease or address it only indirectly via diabetes and hypertension targets [2]. There is now a push from the nephrology community to change this. The International Society of Nephrology (ISN) and other advocacy groups have called for CKD to be recognized as a priority condition within the global NCD. The ISN is working closely with WHO as an official partner (non-state actor in official relations) to advance kidney health. From 2021-2023, ISN and WHO collaborated on a plan delivering several research and advocacy projects focused on the global burden of kidney diseases and how to integrate CKD into NCD strategies. One tangible output from an earlier ISN-WHO collaboration is the ISN Global Kidney Health Atlas, a comprehensive survey of kidney care capacity across 160+ countries, which has highlighted significant gaps in workforce, services, and funding for CKD in many regions [2]. Another is the ISN's framework for developing dialysis programs in low-resource settings, published with WHO support, which provides guidance to countries on expanding dialysis access. Importantly, momentum is building for a formal WHO resolution on kidney disease. At the 2025 World Health Assembly, kidney health advocates (including ISN) are organizing discussions on "Kidney Health as a Policy Imperative" to urge member states to adopt a resolution that would elevate CKD on par with other NCDs. Such a resolution could catalyze governments to devote greater attention and resources to CKD prevention and care as part of their commitments to Universal Health Coverage and the Sustainable Development Goals.

National policies and programs

Some forward-looking countries have implemented dedicated programs to combat CKD, often embedded in broader NCD strategies. As mentioned, Taiwan's nationwide CKD program is a model of success, showing that policy-backed early intervention can bend the curve of kidney failure incidence [18]. Japan has long included urinalysis for proteinuria in its routine health check-ups for adults, which facilitates early detection of kidney disease. In the United States, CKD has received increased policy focus in recent years: the U.S. CDC's CKD Initiative was established to provide public health strategies for kidney health, including surveillance of CKD prevalence and promoting early detection. In 2019, the U.S. government announced the "Advancing American Kidney Health" initiative, setting ambitious goals to reduce the number of Americans developing end-stage kidney disease, expand home dialysis use, and increase kidney transplants [19]. This initiative has led to new payment models that incentivize preventive nephrology care and transplantation. For example, Medicare now offers Kidney Health Education for CKD stage 4 patients and has implemented pilot programs that reward healthcare providers for keeping CKD patients off dialysis by optimally managing their care. In Europe, several countries (e.g. the UK, Netherlands) have integrated CKD screening and management protocols into primary care and have quality indicators tracking CKD care. However, as a whole the policy response in Europe has been uneven – an EU-wide NCD initiative for 2022-2027 did not specifically address CKD [5], reflecting that kidney disease still flies under the radar in some policy frameworks. In many low- and middle-income countries, national CKD programs are rudimentary or nonexistent. Patients often rely on general NCD clinics (if they exist) or hospitals that provide dialysis with variable government support. One encouraging development is that some LMIC governments are beginning to include dialysis in public insurance packages or subsidize it. For instance, India launched a National Dialysis Program to provide free dialysis in district hospitals, and Thailand covers dialysis under its Universal Coverage Scheme. But funding constraints mean that in numerous countries, only a fraction of patients who need KRT actually receive it [20, 21]. Expanding equitable access to CKD care remains a pressing policy challenge.

Health system reforms and integration

Experts have emphasized that combating CKD requires health system strengthening, particularly at the primary care level. Since CKD intersects with other chronic diseases, a vertical approach is less effective than integrated chronic care models. One proposed solution is the adoption of integrated kidney care – a framework that links prevention, early detection, and management of CKD with the treatment of kidney failure in a continuum [22]. Instead of focusing solely on costly end-stage treatment, integrated kidney care calls for coordinating all levels of intervention: community-based prevention, primary care management of early CKD, and accessible dialysis/transplant services, with smooth transitions between these levels [22]. This approach also stresses the efficient use of resources; for example, prioritizing transplantation or peritoneal dialysis over hemodialysis where feasible, and considering conservative (non-dialysis) care for patients unlikely to benefit from dialysis. Health policy can facilitate integrated care by breaking down silos between specialties and care settings. In practice, this means developing clinical pathways that involve primary care physicians in CKD management (with support from nephrologists), setting up regional CKD care networks, and using e-health tools for consultation and monitoring. Payment reform is another key lever – current reimbursement systems in many countries incentivize dialysis (e.g.,

through fee-for-service payments for each dialysis session) more than preventive care. Shifting incentives upstream (such as capitated or bundled payments that reward keeping patients stable without dialysis) can motivate providers to invest in prevention. Some countries are experimenting with such models: for instance, integrated care bundled payment pilots in the U.S. and risk-sharing contracts in Europe that hold providers accountable for renal outcomes. Universal health coverage (UHC) is crucial to alleviate the financial barrier for patients; coverage of CKD services (from blood pressure medications to dialysis) under public insurance or UHC packages can prevent catastrophic health expenditures. Brazil's constitutionally guaranteed universal health system (SUS) covers dialysis for eligible patients – as of 2019, about 79% of Brazilian dialysis patients had their treatment funded by SUS. Still, many nations have yet to provide such safety nets, resulting in inequitable access. Expanding UHC to include essential CKD care (as recommended by WHO) is a vital policy goal [2].

Education, awareness, and guidelines

Another important facet of policy response is improving awareness of CKD among health professionals and the public. Lack of awareness is a major barrier – both patients and providers often underestimate CKD until advanced stages. Public education campaigns (such as the annual World Kidney Day spearheaded by international kidney organizations) aim to raise awareness about kidney health and encourage screening for those at risk. At the provider level, clinical practice guidelines have been developed to standardize CKD care. The Kidney Disease: Improving Global Outcomes (KDIGO) initiative, an international collaboration, has published evidence-based guidelines on CKD evaluation, blood pressure management, diabetes management in CKD, etc., which serve as reference standards worldwide. Many countries have adapted these into local guidelines or care protocols. Implementation of guidelines in primary care is being pursued through continuous medical education and decision-support tools (for example, prompting doctors to check renal function annually in diabetics). Health systems are also investing in health information technology to improve CKD care, such as electronic medical record alerts for abnormal kidney function and better coding of CKD diagnoses. Removing the stigma and therapeutic nihilism around CKD is part of the cultural change needed – clinicians must recognize that diagnosing CKD early does make a difference, because there are interventions that can slow progression and reduce complications. In summary, effective policy responses to CKD span a wide range: from high-level recognition and inclusion in national health plans, to very practical measures like training primary care staff, financing essential services, and leveraging new therapies (e.g. ensuring affordable access to SGLT2 inhibitors which have been shown to benefit CKD patients.

Encouragingly, some recent initiatives are breaking down traditional boundaries of care. For instance, multi-sectoral efforts addressing CKD alongside diabetes and hypertension in community programs have shown promise. Innovative delivery models, such as mobile clinics providing screening in remote areas and community health workers following up CKD patients at home, are being tried in parts of Asia and Africa. These efforts seek to overcome barriers like geographical access and workforce shortages. Telemedicine is also playing a role in linking specialists to primary care in underserved regions for CKD management advice. Overall, while the policy response to CKD has historically lagged, a shift is underway. The convergence of growing disease burden data, economic imperatives, and advocacy is pushing CKD higher on the agenda. Moving forward, sustained political will and resource allocation will be needed to implement these strategies on a broad scale.

Conclusions

CKD has firmly emerged as a global public health threat – one that demands the same level of urgency and coordinated action as other major chronic diseases. The evidence presented highlights that CKD prevalence is high and rising worldwide, with millions of individuals affected and significant mortality that continues to increase despite advances in other health areas. The disease carries devastating personal consequences for patients and families, and its financial costs are straining health systems everywhere. Yet, CKD remains under-diagnosed and under-prioritized. The good news is that CKD is to a large extent preventable, or at least its progression can be delayed, through well-known interventions: effective control of diabetes and hypertension, lifestyle modifications, and early use of reno-protective therapies. We already have the knowledge and tools to make a substantial impact on the CKD burden. What is needed is the political commitment and smart allocation of resources to put these tools into practice on a population level. This means integrating kidney health into national NCD programs, investing in primary care and screening infrastructure, and ensuring that patients have access to affordable treatment and specialist care when needed. International and national initiatives are beginning to rise to the challenge – from WHO's engagement and the ISN's advocacy, to successful country programs that can be emulated. Healthcare professionals have a critical role in this effort: by following clinical guidelines, raising awareness, and participating in multidisciplinary strategies, they can help bridge the implementation gap. In conclusion, CKD exemplifies a modern public health paradox: a condition that is common, harmful, and largely preventable, yet still not adequately addressed. Recognizing CKD as a major public health problem is the first step; the next is translating that recognition into concrete actions in policy and practice. With concerted action now, we can curb the trajectory of CKD, save countless lives, and reduce the tremendous societal costs associated with this disease in the years to come.

Competing interests

None declared.

Authors' contributions

All authors contributed equally to the research, data analysis, and writing of the manuscript. All authors read and approved the final article.

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CASE STUDY

COVID-19 as a possible risk factor for poor prognosis in systemic sclerosis

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ABSTRACT

Introduction. Scleroderma Renal Crisis (SRC) is a life-threatening complication of systemic sclerosis (SSc), traditionally associated with anti-RNA polymerase III antibodies, corticosteroid use, and diffuse skin involvement. However, the role of COVID-19 as a potential trigger for SRC remains poorly understood. This study explores the occurrence of COVID-19-associated SRC, focusing on its clinical presentation, underlying risk factors, and outcomes.

Case presentation. We present a case series of two unvaccinated patients with systemic sclerosis who developed SRC following COVID-19 infection, despite the absence of traditional risk factors. Clinical features, laboratory findings, renal histopathology, and disease progression were analyzed to assess potential mechanisms linking SARS-CoV-2 infection to SRC onset. Both patients developed abrupt-onset malignant hypertension and acute kidney injury after supporting the COVID-19. Neither patient had a history of corticosteroid use or known anti-RNA polymerase III positivity, suggesting an alternative mechanism of SRC activation. Notably, both cases had pre-existing renal anomalies (renal developmental abnormality and prior nephrectomy), which may have contributed to increased susceptibility. Despite aggressive management, both patients developed dialysis-dependent renal failure and succumbed to SRC-related complications.

Conclusions. Our findings highlight COVID-19 as a potential trigger for SRC, possibly through endothelial dysfunction, inflammatory cytokine storms, and renal microangiopathy. The presence of pre-existing kidney conditions may further predispose SSc patients to SRC following SARS-CoV-2 infection. Additionally, the lack of vaccination in these cases raises the question of whether COVID-19 immunization could reduce SRC risk. Further research is needed to elucidate the pathophysiology, risk stratification, and long-term outcomes of COVID-19-associated SRC, as well as the role of vaccination in prevention.

Keywords: COVID-19, scleroderma renal crisis, systemic sclerosis, acute kidney injury, SARS-CoV-2.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Currently, the influence of COVID-19 infection on the evolution and prognosis of systemic sclerosis, as well as the role of anti-covid vaccination in preventing major complications, is unknown.

The research hypothesis

COVID-19 infection exacerbates the progression of systemic sclerosis and serves as a potential trigger for scleroderma renal crisis, particularly in patients with pre-existing kidney conditions.

The novelty added by the manuscript to the already published scientific literature

The manuscript contributes to the understanding of COVID-19 infection as a trigger factor for renal complications in systemic scleroderma and indicates the need to study the role of anti-covid vaccination to reduce severe complications of the disease.

Introduction

Systemic sclerosis (SSc) is an autoimmune, multisystem connective tissue disorder marked by extensive vascular dysfunction and the gradual development of fibrosis in the skin as well as internal organs, including kidneys [1]. The most severe manifestation of renal involvement in systemic sclerosis is the scleroderma renal crisis (SRC), an infrequent complication. The reported incidence is 7-9% in individuals with diffuse SSc and 5-6% in those with the limited SSc [2]. The pathogenesis of SRC involves endothelial damage, intimal proliferation, and the constriction of kidney arteries, resulting in reduced renal blood flow. This sequence of events induces hyperplasia of the juxtaglomerular apparatus, consequently elevating renin levels leading to acute hypertension and renal dysfunction [3].

COVID-19, caused by SARS-CoV-2, has disproportionately impacted individuals with underlying autoimmune conditions due to their increased susceptibility to infection and disease exacerbation. The SARS-CoV-2 virus has shown a direct and indirect impact on kidney function through mechanisms such as viral invasion of renal cells, hyperinflammation, and vascular injury [4]. These overlapping pathophysiological pathways raise concerns about worse outcomes in SSc patients affected by COVID-19. SARS-CoV-2 targets the kidneys via angiotensin-converting enzyme 2 (ACE2) receptors, leading to direct cytotoxicity, endothelial dysfunction, and microvascular thrombosis [5]. These mechanisms overlap with the vascular pathology seen in SSc, exacerbating renal damage. The impact of COVID-19 infection on the development of kidney damage is well-documented. Common kidney biopsy findings associated with COVID-19 include acute tubular damage, collapsing glomerulopathy (a variant of focal segmental glomerulosclerosis, and thrombotic microangiopathy. Additionally, acute tubular injury is frequently observed in COVID-19 patients with acute kidney injury (AKI). Several glomerular diseases have been linked to COVID-19 infection, encompassing crescent glomerulonephritis, minimal change disease, focal segmental glomerulosclerosis, vasculitis (including anti-neutrophil cytoplasmic antibody-associated vasculitis, anti-glomerular basement membrane disease, and immunoglobulin A vasculitis with nephritis), membranous nephropathy, lupus nephritis, and acute tubular injury. Furthermore, mixed pathologic renal lesions, acute interstitial nephritis and treatment-related AKI have been reported in COVID-19 patients [6-8].

Moreover, a case report has documented the onset of systemic sclerosis subsequent to a mild COVID-19 infection in a previously healthy individual. The authors proposed that there are certain parallels between COVID-19 infection and systemic sclerosis [9]. Exposure to corticosteroids at doses exceeding 15 mg (frequent use in the treatment scheme for COVID-19 infection) per day in the preceding 6 months is a major recognized risk factor [10].

Ferri *et al.* (2021) assumed the virus might exacerbate pre-existing manifestations of systemic sclerosis during the acute phase of COVID-19 infection. However, over the long term, this interaction could potentially lead to complex organ damage [11].

Cases presentation

Patient no. 1

A 46-year-old female presented with symptoms indicative of SSc, beginning in May 2016. Clinical manifestations included edema affecting the hands and face, cutaneous thickening extending to the knees with associated flexion difficulties, and a concomitant esophageal burning sensation. In June 2016, the onset of Raynaud's phenomenon, characterized by pallor in the digits, further prompted clinical evaluation. Diagnostic workup revealed positive ANA and ATA antibodies, with negative anti-RNA polymerase III antibodies. Methotrexate, 10 mg/week and Amlodipine, 10 mg/day was started, this leading to an improvement in her overall condition.

In December 2019, she was diagnosed with viral hepatitis. At the same time, lung CT presented pulmonary fibrosis with multiple ground-glass opacities. She received antiviral treatment with Tenofovir 300 mg daily, and in March 2020 treatment with Cyclophosphamide therapy was initiated at 1000 mg, intarvenously once a month, which was then stopped due to the pandemics.

On November 10, 2020, the patient presented symptoms indicative of an acute respiratory viral infection, and a subsequent PCR test confirmed COVID-19 infection. She was admitted to the hospital, and received treatment included antiviral, antibacterial medications, and glucocorticosteroids (Methylprednisolone up to a maximum of 12 mg/day), and symptomatic care. The patient's general condition deteriorated, with the onset of muscle weakness, diarrhea, and worsening dyspnea. On December 10, 2020, a chest CT scan revealed diffuse areas of pulmonary tissue induration with bilateral ground-glass opacities. Additionally, a *Clostridium difficile* infection was detected, leading to the initiation of antibiotic therapy. The patient continued treatment with Methylprednisolone at a reduced dosage of 8 mg/day, vasodilators, and symptomatic care.

Throughout 2021, the patient experienced progressive skin involvement characterized by thickening in the arms, forearms, chest, and thighs, accompanied by worsening respiratory function. Gastrointestinal involvement also progressed, and Raynaud's syndrome persisted. Treatment with methylprednisolone at a reduced dosage of 4 mg/day, vasodilators and proton pump inhibitors was continued.

Chest CT repeated on 09.02.2022 showed disease progression with an increase in fibrotic changes, multiple ground glass and paving stone opacities, some cylindrical bronchiectasis, dilation of the esophagus. During this period, the patient underwent immunosuppressive therapy with Cyclophosphamide 1000 mg, alongside maintenance medications including Methylprednisolone at 4 mg/day, Amlodipine at 10 mg/day, and Pantoprazole at 20 mg/day. Unfortunately, there was no discernible improvement. Subsequently, Azathioprine was recommended as an alternative, but it was discontinued after two weeks due to adverse reactions, including general weakness, dizziness, and visual disturbances. Regrettably, the patient's condition continued to deteriorate progressively.

During the patient's most recent hospitalization spanning from April 4, 2023, to April 10, 2023, a comprehensive examination was conducted, yielding the following results:

Physical examination: diffusely hyperpigmented skin, Rodnan score 46, telangiectasias on the face and chest, mod-

erate leg edema, bilateral harsh breath sounds on auscultation, with fine basal bilateral crackles, respiratory rate: 19 breaths/minute, SpO_2: 93% on room air, Blood pressure - 180/110 mmHg, periodically increasing to 240/140 mmHg; heart rate: 82 bpm; dry, coated tongue, liver palpable +3-4 cm; Diuresis measured at 400 ml/24 hours.

Laboratory and imagining findings: leukocytosis, reticulocytosis, Creatinine - 451.2 - 623.7 - 540.4 – 534.2 mmol/l; Uric acid - 611.3 mmol/l; Urea - 33.02 mmol/l; Proteinuria - 10 g/l; clear urinary sediment.

Kidney ultrasound: asymmetrically renal positioning, left kidney displaced to the lumber region; horseshoe kidney on the right measuring 90x40 mm; left kidney 96x40 mm, mildly deformed bilateral pelvicalyceal system.

Treatment: glucocorticosteroid (Methylprednisolone 4 mg/day); histamine 2 receptor antagonists (Famotidine); calcium channel blockers (Amlodipine); angiotensin converting enzyme inhibitors (Ramipril), synthetic prostaglandin analog (Alprostadil); diuretics (Torasemide).

Disease progression: on April 11, 2023, the patient was discharged from the hospital at her own request, and 2 days later had died at home.

Patient no. 2

A 67-year-old female with no prior history of rheumatic pathology presented with symptoms in November 2021, including inflammatory arthralgia in the small joints of the hands bilaterally and paresthesia. The patient initially used NSAIDs and local ointments, resulting in subsequent improvement. In December 2021, she developed an acute respiratory viral infection marked by low-grade fever, sore throat, and a runny nose. Following a positive PCR test for COVID-19 infection, she received symptomatic treatment at home. After recovering from the SARS-CoV-2 infection, the patient observed the onset of edema in the hands, progressing to the forearms and the lower third of the arms. Subsequently, swelling occurred on the shins, thighs, and lower abdomen. From the patient's personal history, she underwent a left kidney nephrectomy 20 years ago due to suspected neoplasia, though the specific diagnosis was not clarified.

In May 2022, the patient sought consultation with a rheumatologist, reporting the aforementioned complaints, including arthralgia in the small joints of the hands, scapulo-humeral, hip, and knee joints, muscle weakness, xerostomia, difficulty swallowing, exertional dyspnea, and pronounced general weakness. A comprehensive evaluation revealed the following: ANA (Antinuclear Antibody): 1/5120; Anti-Scl70 – positive; anti-RNA polymerase III antibodies – negative. The diagnosis of active diffuse systemic sclerosis (EUSTAR score = 5 points) was established. Treatment was initiated with Methylprednisolone 4 mg/day, Azathioprine 100 mg/day, and Nifedipine 10 mg/day. However, the patient demonstrated poor compliance with the prescribed treatment..

Over time, the patient's symptoms, including arthralgia, myalgia, general weakness, and generalized peripheral edema, along with uncontrolled hypertension, escalated. Consequently, she was admitted to hospital from September 20, 2022, to October 4, 2022, with suspected scleroderma renal crisis. Objective findings during the examination included scleroderma manifestations such as indurated skin on the hands, forearms, arms, thighs, and legs (Rodnan score 38), with hands exhibiting flexion contractures and digital ulcers. Telangiectasias were observed on the face, chest, and flanks, along with microstomia. Auscultation revealed harsh breath sounds, subcrepitant and crepitant rales at the base. Blood pressure measuring 200/96 mmHg, and a heart rate of 80 bpm were noted. The patient reported frequent urination and nocturia.

Blood tests indicated the following deviations: leukocytosis and anemia, azotemia (creatinine 1017 mmol/l, urea 56 mmol/l, hyperkalemia - 7.02 mmol/l). Bacteriological examination of urine indicated hemolytic *E. coli* with a titer of 10^7. Blood bacteriological examination was sterile. Esophagus radioscopy revealed mucosal smoothing and reduced peristalsis, and a chest X-ray disclosed bilateral pleurisy with pleural effusion from ribs 5 to the diaphragm.

The patient underwent an evaluation by a nephrologist, leading to the diagnosis of Scleroderma renal crisis and chronic kidney disease. Hemodialysis sessions were initiated, but the patient poorly tolerated the procedure, experiencing apathy and mild confusion.

The patient was transferred to the intensive care unit due to a worsening general condition, leading to cardiogenic obstructive shock, severe left ventricular outflow tract obstruction and respiratory failure. Pneumonia by stasis and bilateral pleurisy were noted.

Despite antibiotic therapy, antihypertensives (including angiotensin converting enzyme inhibitors, calcium channel blockers, and diuretics), and anticoagulants, the patient's condition deteriorated. On the fourth day of hospitalization, the patient became anuric despite adequate intravenous fluid hydration and diuretic therapy, and edema progressed to anasarca. Hemodialysis sessions were initiated, resulting in a positive trend in urea and creatinine levels. Although the patient remained hemodynamically stable without vasopressor support, respiratory failure ensued, necessitating O_2 therapy at 6 l/min via a simple face mask. By the tenth day, assisted ventilation became necessary. A chest X-ray revealed alveolar pulmonary edema in subtotal bilateral pleuropneumonia, alongside bilateral pleurisy. A diagnosis of uro-nephrogenic, pulmonary septic shock was established, with subsequent progression to septic MODS and end-stage renal disease. The disease trajectory turned negative due to toxicoseptic shock, febrile syndrome, and significant leukocytosis. On the fifteenth day of hospitalization, the patient experienced cardiac arrest due to asystole, occurring in the context of mechanical ventilation and high doses of catecholamines.

Discussions

Scleroderma renal crisis (SRC) is a rare but potentially devastating complication of systemic sclerosis as it is associated with significant morbidity and mortality.

SRC classically develops in patients with early or progressive diffuse cutaneous disease or positivity for anti-RNA polymerase III antibodies. Other risk factors for SRC are pericardial effusion, tendon friction rub and steroid use. COVID-19 has been reported to cause TMA by inducing immune dysregulation via an overactive complement system. It is plausible that infection with COVID-19 triggered an exaggerated immune response, in turn leading to the development of SRC

in our patient. COVID-19 may trigger SRC in patients with systemic sclerosis in the absence of other risk factors.

Salman Mahmood *et al.* have presented case of a 37-year-old female patient who did not have any such risk factors and rather developed SRC following infection with COVID-19 leading to dialysis dependence [7]. Described patients were also negative for anti-RNA polymerase III antibodies, but still suffered from the diffuse form of the disease and one of them was in the early phase of the disease.

Doron Rimar *et al.* have reported a case of scleroderma renal crisis (SRC), following COVID-19 infection, in a limited-SSc patient who was in long remission prior to the infection without any risk factors for SRC [6]. The temporal relationship and lack of other risk factors combine to suggest COVID-19 infection as a possible trigger for SRC. Authors have discussed the shared pathophysiology of COVID-19 infection and SRC, including, vasculopathy, endothelial activation, hypercoagulability, cytokines release as interleukin 6, that may explain the possible role of COVID-19 infection, as a trigger for SRC in SSc patients.

Despite the fact that our patients have not been vaccinated against COVID-19, there are reported cases of kidney injury following vaccination for coronavirus disease 2019 (COVID-19) with a focus on renal pathology. One review published in 2022 have found 49 case reports [12]. These included minimal change disease (n = 17), IgA nephropathy (IgAN) (n = 15), IgA nephritis/vasculitis (n = 5), ANCA glomerulonephritis/vasculitis (n = 5), anti-glomerular basement membrane (GBM) nephritis (n = 2), and 1 case of each granulomatous vasculitis, acute tubulointerstitial nephritis, scleroderma renal crisis, IgG4-related disease nephritis, and primary membranous nephropathy (MN). Further investigations of the underlying pathogenesis of post-COVID-19 vaccination renal adverse events are required.

Exposure to corticosteroids can trigger scleroderma renal crisis. A case was reported involving a female patient who developed systemic sclerosis post-COVID-19 infection. Following exposure to corticosteroids, the patient developed scleroderma renal crisis complicated by thrombotic microangiopathy, seizures and acute renal failure. Despite an antibody profile not typically associated with renal crisis (anti-topoisomerase positive, anti-RNA- polymerase III negative), the patient developed recurrent renal crisis with repeated exposure to corticosteroid therapy, highlighting the risk of steroid use in all patients with systemic sclerosis [10]. Our patients were treated with glucocorticosteroids, but in low doses, which may not be considered a risk factor for the development of SRC.

A common feature in both presented cases were the pre-existing kidney diseases (in the first patient - congenital anomaly of the kidneys and in the second - unilateral nephrectomy) which can also be considered risk factors for SRC in patients who have suffered from COVID-19.

Conclusions

In both of the presented cases, COVID-19 infection worsened the progression of systemic sclerosis and ultimately led to the death of the patients through the development of scleroderma renal crisis. Of all the known risk factors for scleroderma renal crisis, the described patients presented only the diffuse form of the disease. Additionally, the presence of pre-existing kidney abnormalities—congenital anomalies in the first patient and unilateral nephrectomy in the second—may also be considered potential risk factors for the development of SRC in individuals with systemic sclerosis who have experienced COVID-19 infection.

Competing interests

None declared.

Authors' contribution

SA, SP, ER conceptualized and designed the study. SA, SP, LR, ER, LD, IM, VS conducted patients and collected their data. SA drafted the manuscript. SP supervised the project and reviewed the manuscript. All authors read and approved the final version of the manuscript.

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ANNIVERSARY

Professor Victor Botnaru – 70 years of excellence in medicine and education

Upon reaching the distinguished age of 70, Professor Victor Botnaru remains an emblematic figure in the field of medicine in the Republic of Moldova. A Habilitated Doctor in Medical Sciences, Professor Botnaru has devoted his entire life to research, education, and the advancement of medical practice, contributing significantly to the progress of pulmonology and internal medicine.

Born on July 6, 1955, in Cinișeuți, Rezina, Professor Botnaru followed an impressive academic path. He earned his PhD in Medical Sciences in 1980 at the Cardiology Center in Moscow, specializing in cardiology and nuclear medicine. In 1991, he defended his habilitation thesis, further establishing his status as an expert in the medical community. Since 1996, he has held the position of Head of the Department of Internal Medicine at the "Nicolae Testemițanu" State University of Medicine and Pharmacy from the Republic of Moldova, which was later reorganized into the Discipline of Pulmonology and Allergology.

Professor Botnaru is not only a remarkable scientist but also a dedicated mentor and educator. Throughout his teaching career, he has trained thousands of students, who now work in various branches of medicine both in Moldova and abroad. Through his innovative teaching methods and motivational approach, he has succeeded in imparting not only theoretical knowledge but also core values such as ethics, responsibility, and devotion to the profession.

As the author and co-author of over 420 scientific works, Professor Botnaru has had a profound impact on the development of generations of students and medical specialists. His medical textbook, including *Pulmonology*, *Imaging in Commented Clinical Cases*, and *Elements of Immunology*, are fundamental references for the academic community and practitioners alike. His works have been recognized both nationally and internationally, contributing to the continuous development of knowledge in the medical field. In addition, he has participated in the drafting of important medical guidelines and protocols that are used as standards in current medical treatments.

As a doctoral advisor, Professor Botnaru has supervised ten successfully defended doctoral theses and three habilitation theses, supporting the formation of prestigious researchers and specialists. Under his guidance, doctoral students have tackled innovative topics, making valuable contributions to the diagnosis and treatment of respiratory diseases. He has also contributed to the organization and support of national and international scientific conferences, facilitating the exchange of experience among specialists from various medical fields.

As an exceptional physician, Professor Botnaru has demonstrated unwavering dedication to his patients and an innovative approach to medical practice. His contributions to modernizing diagnostic and treatment methods in pulmonology have significantly improved the quality of healthcare in Moldova. He has also been involved in multiple international research projects, such as The European Bronchiectasis Registry and the Global Consortium for Drug-resistant Tuberculosis Diagnosis. Through these collaborations, he has brought advanced diagnostic and treatment methods to Moldova, helping raise the standards of the national medical system.

In recognition of his outstanding merits, Professor Victor Botnaru was awarded the State Prize of the Republic of Moldova in the field of science, technology, and production (1994) and the honorary title of "Merited Person of the Republic of Moldova" (2015). These distinctions underscore his remarkable contribution to the development of medicine and medical education. His expertise continues to be sought in prestigious commissions and working groups.

Beyond his exceptional professional activity, Professor Botnaru is a man of integrity, a respected colleague, and a devoted friend. Those who know him describe him as an open person, always willing to help, offer advice, or provide guidance. His passion for medicine is matched only by his devotion to his family and students.

On this anniversary, the medical and academic community extends to Professor Victor Botnaru the warmest congratulations, gratitude, and wishes for health, prosperity, and continued success in his prodigious career. May he continue to be an example and a source of inspiration.

Happy birthday, Professor!

Emil Ceban, rector of the *Nicolae Testemițanu* SUMPh
Dr. hab. med. sciences, university professor,
corresponding member of the ASM

MONOGRAPH REVIEW

„Health status of employees in meat processing enterprises and preventive measures”

Authors: Iurie Pînzaru, Grigore Friptuleac, Agripina Rașcu

Monograph details: Pînzaru I, Friptuleac G, Rașcu A. Starea de sănătate a angajaților întreprinderilotr de procesare a cărnii și măsurile de profilaxie [Health status of employees in meat processing enterprises and preventive measures]. Chișinău; 2024. 259 p. ISBN 978-9975-57-369-6. Romanian.

A new viewpoint on occupational hygiene in the meat processing sector is presented in the monograph „Health status of employees in meat processing enterprises and preventive measures”, written by Iurie Pînzaru, PhD, associate professor, Grigore Friptuleac, PhD, university professor, and Agripina Rașcu, university professor. The most recent study findings about the effects of various occupational risk factors on workers’ health are presented, both on the authors’ research and on studies by other scholars.

In this regard, the monograph offers a thorough hygienic evaluation of the work procedures and technology used in meat processing enterprises. In addition to assessing occupational risk factors identified in the workplace, the authors also highlight the characteristics, health status, and the functional state of workers involved in the primary technical phases. After their comprehensive review, the authors propose workplace health policies, detailing certain preventative techniques and actions. The monograph concludes with models of occupational health service models, which are crucial for developing new occupational health concepts, strategies, and policies.

Thus, the theoretical foundation laid by this work has clear practical significance. An important portion of the research presented in the monograph is original and can serve as a model for studies in other areas of hygiene. Optimizing working conditions to reduce occupational risk factors is crucial and represents one of the main ways to increase efficiency of the meat processing industry. Besides boosting productivity, this strategy also helps to maintain and improve employees’ health.

For the first time, the authors have conducted a comprehensive hygienic assessment of the technological and operational procedures in meat-processing enterprises, evaluated employees’ health status, and analyzed the occupational risk factors in this industry. Based on their findings, they have developed specific workplace prevention strategies and occupational health service models.

The monograph’s content is fully aligned with the ten essential public health operations recommended by the World Health Organization, as well as the current national and international plans for the development of workplace-health policies. The study gains more confidence due to the substantial number and complexity of laboratory experiments and procedures performed.

From both scientific and practical standpoints, the monograph “*Health status of employees of meat processing enterprises and preventive measures*” is a unique and significant work that addresses contemporary public health issues.

This monograph will serve as a valuable reference for occupational hygiene and health specialists, labor inspection authorities, students of the *Nicolae Testemițanu* State University of Medicine and Pharmacy, as well as industry managers and professional associations in the meat processing sector.

Ion Bahnarel, PhD, university professor
Hygiene Discipline, Department of Preventive Medicine
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[Revised May, 2023]

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In-text reference citations should be numbered consecutively, identified by Arabic numerals in square brackets [ ]. References should be listed at the end of the manuscript and numbered in the order in which they are first mentioned in the text. Every reference cited in the text is also present in the reference list (and vice versa). Journals titles should be abbreviated according to the Index Medicus.

It may be cited only articles or abstracts that have been published and are available through public servers. Personal communications, manuscripts in preparation, and other unpublished data should not be included in the reference list, but may be mentioned in parentheses in the text as "unpublished data" or "unpublished observations", indicating the involved researchers. It is of manuscript authors' responsibility to obtain the permission to refer to unpublished data.

The references in the Cyrillic, Greek, Arabic scripts should be transliterated into Latin script using the ALA-LC Romanization Tables.

Non-English titles must be followed by the English translation in square brackets.

All electronic references should include active and available URLs and the access date.

Examples of references

Journal article

Belîi A, Cobâleţchi S, Casian V, Belîi N, Severin G, Chesov I, Bubulici E. Les aspects pharmacoéconomiques dans la gestion de la douleur périopératoire [Pharmaco-economic aspects of perioperative pain management]. Ann Fr Anesth Reanim. 2012;31(1):60-6. French. doi: 10.1016/j.annfar.2011.09.008.

Book

Razin MP, Minaev SV, Turabov IA. Detskaia khirurgiia [Pediatric surgery]. 2nd ed. Moscow: Geotar-Media; 2020. 696 p. Russian.

Chapter in a book

Steiber AL, Chazot C, Kopple JD. Vitamin and trace element needs in chronic kidney disease. In: Burrowes J, Kovesdy C, Byham-Gray L, editors. Nutrition in kidney disease. 3rd ed. Cham: Humana Press; 2020. p. 607-623.

Conference paper

Ojovan V. Medical rehabilitation of children with type 1 diabetes: medical bioethical and psychosocial aspects. In: MedEspera: 9th International Medical Congress for Students and Young Doctors, 12-14 May 2022, Chisinau, Republic of Moldova: Abstract book. Chișinău; 2022. p. 77.

Website reference

World Health Organization (WHO). Therapeutics for Ebola virus disease [Internet]. Geneva: WHO; 2022 [cited 2022 Sep 5]. Available from: https://www.who.int/publications/i/item/9789240055742

TABLES AND FIGURES

Tables should be numbered consecutively with Arabic numerals, and be cited in text. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Tables must be submited as editable text and not as images. Each table should be completely informative in itself, and the data presented in it do not duplicate the results described elsewhere in the article.

The label "Table 1" and a short descriptive title should be provided above the table. Legends, notes, and any abbreviations used in the table should be explained below the table in a footnote. Applied statistical tests and the type of presented data should be also mentioned. Please follow the example:

Table 1. Intra-anesthetic and immediately post-extubation adverse events

	Experimental Cohort (n=100)	Control Cohort (n=100)	p
Dysrhythmia	6.0%	30%	0.49
Hemodynamic instability	7.0%	1.0%	0.034
Prolonged awakening*	11.0%	4.0%	0.19
PONV post-intubation	8.0%	27.0%	0.007
Strong pain on awakening	17.0%	19.0%	1.0

Note: *Unusually slow awaking, after that cerebral concentration of the anesthetic reach the under hypnotic level.
Used statistical analysis: Fisher's exact test.

Figures (photographs or radiographs, drawings, graphs, bar charts, flow charts, and pathways) should be submitted in a suitable format for print publication. Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. Figures' quality should assure the visibility of details. The following file formats are accepted: ".jpeg", ".tiff", ".eps" (preferred format for diagrams), ".ppt", ".pptx" (figures should be of the size of a single slide), with a resolution of at least 300 dpi.
Figures will be included in the main manuscript, and also submitted as separate files. The file title should include the figure number and an identifiable short title.
Figures should be numbered consecutively according to the order in which they have been cited in the text. Write the label **Fig. 1** and a short descriptive title under the figure. Figure's legend should describe briefly the data shown. Figure's description should not repeat the description in the text of the manuscript. When used symbols, arrows, numbers or letters to describe parts of the figure, explain clearly each one of them in the legend. Explain the internal scale and identify the staining method of the photomicrographs.
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3. final approval of the version to be published; AND
4. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data access and responsibility

The corresponding author should indicate that he or she had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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15 **EFECT ANALGEZIC PESTE 15 MINUTE[4]**

Brufen 600 mg în granule efervescente[1]

ACȚIONEAZĂ MAI RAPID DECÂT COMPRIMATELE[5]

Brufen 600 mg granule efervescente.

Certificat de înregistrare în Republica Moldova: nr. 30498 din 04.12.2024. Compoziție: 1 plic conține ibuprofen 600 mg. Indicații terapeutice: tratarea artritei reumatoide, inclusiv artritei reumatoide juvenile sau bolii Still, spondilitei anchilozante, osteoartritei și altor artropatii nereumatoide (seronegative) și artritei gutoase acute; tratamentul afecțiunilor reumatice nearticulare și a afecțiunilor periarticulare, precum sindromul umărului înghețat (capsulita), bursita, tendinita, tendosinovita și a durerilor lombare; în traumele țesuturilor moi, precum luxațiile și entorsele, pentru atenuarea durerilor ușoare și moderate, precum dismenoreea primară, durerile dentare sau postoperatorii, durerea după episiotomie, durerea după naștere și pentru atenuarea simptomatică a durerilor de cap, inclusiv a migrenelor; tratamentul febrei. Doze și mod de administrare: - Adulții și adolescenții cu vârsta peste 12 ani (≥ 40 kg): doza zilnică recomandată este de 1200-1800 mg, divizată în câteva prize. Pentru unii pacienți poate fi suficient 600-1200 mg pe zi. În cazuri severe și acute poate fi util de crescut doza până la finisarea fazei acute. Doza zilnică maximă nu trebuie să depășească 2400 mg, care se utilizează în câteva prize. Copii: Brufen în această formă farmaceutică este contraindicat copiilor cu vârsta sub 12 ani. Administrare orală. Pentru a realiza un debut mai rapid al acțiunii, doza poate fi administrată pe stomacul gol. La pacienții cu afecțiuni ale tractului gastrointestinal medicamentul se administrează în timpul mesei. Înaintea administrării granulele trebuie dizolvate într-o cantitate mare de apă. La administrarea medicamentului poate apărea o senzație tranzitorie de arsură la nivelul cavității bucale sau gâtului. Contraindicații: hipersensibilitate la substanța activă sau la oricare dintre excipienți; pacienților cu astm bronșic, urticarie ori reacții de tip alergic în urma administrării de acid acetilsalicilic/aspirină sau alte AINS; insuficiență cardiacă severă (NYHA IV); insuficiență hepatică severă; insuficiență renală severă (rata filtrării glomerulare sub 30 ml/min); afecțiuni care implică o tendință crescută de sângerare sau sângerare activă; antecedente de sângerări gastrointestinale ori perforații, în urma terapiei cu AINS; colită ulcerativă, boala Crohn, ulcer peptic recidivant sau hemoragie gastrointestinală (două sau mai multe episoade distincte de ulcer sau hemoragii diagnosticate) prezente sau în antecedente; trimestrul trei de sarcină. Atenționări și precauții speciale: Reacțiile adverse pot fi minimizate prin utilizarea celor mai mici doze cu efect terapeutic pentru cel mai scurt timp posibil necesar controlului simptomelor. AINS se vor administra cu o precauție deosebită la pacienții cu ulcer peptic și alte afecțiuni gastrointestinale în antecedente, deoarece starea lor se poate agrava. Reacțiile adverse la utilizarea de Ibuprofen nu diferă de alte AINS. Cele mai frecvente reacții adverse observate sunt de natură gastrointestinală. După administrare au fost raportate greață, vomă, diaree, meteorism, constipații, dispepsie, dureri abdominale, melena, hematemeză, stomatită ulceroasă, hemoragii gastrointestinale, acutizarea colitei și bolii Crohn. Se eliberează pe bază de prescripție medicală. Producător: AbbVie S.r.l. S.R. 148 Pontina KM 52, SNC - Campoverde di Aprilia (loc. Aprilia) - 04011 Aprilia (LT), Italia. Data revizuirii textului: Decembrie 2024.

Brufen Rapid capsule moi.

Certificate de înregistrare în Republica Moldova: nr. 26419 și nr. 25420 din 11.08.2020 Compoziție: 1 capsulă conține ibuprofen 200 sau 400 mg. Indicații terapeutice: tratamentul simptomatic pe termen scurt al durerilor ușoare până la moderate, cum sunt cefalee, dureri menstruale, dureri de dinți, durerii asociate simptomelor de gripă și febră la adulți și adolescenți cu greutatea de cel puțin 20 kg (de la vârsta de 6 ani pentru Brufen Rapid 200 mg) și cel puțin 40 kg (de la vârsta de 12 ani pentru Brufen Rapid 400 mg). Doze și mod de administrare. Pentru administrare orală și pe termen scurt. Capsulele nu trebuie mestecate. Brufen Rapid 200 mg: Doza inițială este de 200 mg sau 400 mg ibuprofen. Doza zilnică totală maximă de ibuprofen este de 20-30 mg/kg, divizată în 3-4 prize, cu intervale între administrarea dozelor de 6-8 ore. A nu depăși doza totală de 30 mg/kg într-un interval de 24 ore. Brufen Rapid 400 mg: Adulți și adolescenți ≥ 40 kg (de la 12 ani și peste): doza inițială este de 1 capsulă (400 mg), administrată cu apă. Dacă este necesar, următoarea capsulă poate fi administrată peste 6 ore. A nu se depăși doza zilnică totală de 1200 mg într-un interval de 24 de ore. Atenționări și precauții speciale pentru utilizare: Se recomandă precauție la pacienții cu anumite afecțiuni, care se pot agrava: lupus sistemic eritematos și boala mixtă a țesutului conjunctiv, din cauza riscului crescut de meningită aseptică, tulburări gastrointestinale și boală intestinală inflamatorie cronică, deoarece aceste stări se pot agrava (colita ulcerativă, boala Crohn), tulburări ale funcției renale, sau hepatice. Reacțiile adverse: cel mai frecvent observate sunt cele de natură gastrointestinală. Este risc posibil de meningită aseptică, porfirie intermitentă acută; la persoanele vârstnice crește riscul dezvoltării consecințelor serioase ale reacțiilor adverse, în special hemoragie și perforare gastrointestinală, care pot fi letale; grețuri, vomă, diaree, constipație, balonare, tulburări gastrointestinale, dureri stomacale, tulburări de scaun, vomă cu sânge, colită ulcerativă, exacerbare a bolii Crohn, agravarea simptomelor gastrointestinale, reacții de hipersensibilitate, reacții alergice nespecifice și anafilaxie, tulburări respiratorii obstructive cronice, deoarece pentru acestea există un risc crescut de dezvoltare a reacțiilor alergice. Aceste reacții se pot manifesta ca un episod de astm bronșic, edem Quincke sau urticarie, reacții cutanate grave, unele dintre ele letale, incluzând dermatita exfoliativă și dermatoză buloasă. Contraindicații: hipersensibilitate la substanța activă, antecedente de reacții de hipersensibilitate sub formă de bronhospasm, astm bronșic, rinită, angioedem sau urticarie, asociate cu administrarea acidului acetilsalicilic sau a altor medicamente antireumatoide/antiinflamatoare nesteroidiene (AINS), antecedente de hemoragii gastrointestinale sau perforație, determinate de terapia anterioară cu AINS, ulcer peptic activ sau în antecedente, sau hemoragie (două sau mai multe episoade distincte diagnosticate de ulcer sau sângerări), pacienți cu insuficiență hepatică severă, insuficiență renală severă sau insuficiență cardiacă severă, pacienți cu hemoragie cerebrovasculară sau alte hemoragii active, tulburări de coagulare sanguină sau diateză hemoragică, pacienți cu tulburări hematopoietice de etiologie neprecizată, pacienți cu deshidratare severă (provocată de vărsături, diaree sau aport insuficient de lichid), utilizarea in trimestrul trei de sarcină. În timpul celui de-al treilea trimestru de sarcină utilizarea ibuprofenului este interzisă. Alăptarea - ibuprofenul și metaboliții săi pot trece in concentrații mici in laptele matern. Se eliberează fără prescripție medicală. Producător: Geltec Private Limited, SR. No. 24, 26/3, 27/2, Yadavnahalli, Attibele, Hosur Rd, Bengaluru, Karnataka 562107, India. Data revizuirii textului: Noiembrie 2024.

Informații detaliate privind aceste medicamente sunt disponibile pe site-ul Agenției Medicamentului și Dispozitivelor Medicale (AMDM) http://nomenclator.amdm.gov.md.

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Bibliografie:

1. Rezumatul caracteristicilor produsului medicamentos Brufen 600 mg granule efervescente.
2. Rezumatul caracteristicilor produsului medicamentos Brufen Rapid 400 mg.
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5. Sharma N.K. et.al. Primary Dental Care. 1994. 1(1): 5-8.
6. Accesibil pe linkul https://www.nottinghampost.com/news/nottingham-news/full-story-how-dr-stewart-2508504; data accesării - aprilie 2025.

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KARDATUXAN 20 mg: fiecare comprimat filmat conține: rivaroxaban 20 mg. **Indicații terapeutice:** KARDATUXAN 2,5 mg: Kardatuxan, administrat concomitent doar cu acid acetilsalicilic (AAS) sau cu AAS plus clopidogrel sau ticlopidină, este indicat pentru prevenirea evenimentelor aterotrombotice la pacienții adulți după un sindrom coronarian acut (SCA) cu valori crescute ale biomarkerilor cardiaci.Kardatuxan, administrat concomitent cu acid acetilsalicilic (AAS), este indicat pentru prevenirea evenimentelor aterotrombotice la pacienții adulți care prezintă boală arterială coronariană (BAC) sau boală arterială periferică simptomatică (BAP) cu risc crescut de evenimente ischemice. KARDATUXAN 10 mg: Prevenirea tromboembolismului venoase (TEV) la pacienții adulți care sunt supuși unei intervenții chirurgicale elective pentru substituția șoldului sau a genunchiului.Tratamentul trombozei venoase profunde (TVP) și al emboliei pulmonare (EP) și prevenirea recurenței TVP și a EP la adulți. KARDATUXAN 15 mg: *Adulți:* Prevenirea accidentului vascular cerebral și a emboliei sistemice la pacienții adulți cu fibrilație atrială non-valvulară cu unul sau mai mulți factori de risc, cum sunt insuficiența cardiacă congestivă, hipertensiunea arterială, vârsta ≥75 ani, diabetul zaharat, accidentul vascular cerebral sau atacul ischemic tranzitoriu în antecedente. Tratamentul trombozei venoase profunde (TVP) și al emboliei pulmonare (EP) și prevenirea recurenței TVP și a EP la adulți. *Copii și adolescenți:*Tratamentul tromboembolismului venoase (TEV) și prevenirea recurenței TEV la copii și adolescenți cu vârsta mai mică de 18 ani și cu greutatea cuprinsă între 30 kg și 50 kg după cel puțin 5 zile de la tratamentul anticoagulant parenteral inițial. KARDATUXAN 20 mg: *Adulți:* Prevenirea accidentului vascular cerebral și a emboliei sistemice la pacienții adulți cu fibrilație atrială non-valvulară cu unul sau mai mulți factori de risc, cum sunt insuficiența cardiacă congestivă, hipertensiunea arterială, vârsta ≥75 ani, diabetul zaharat, accidentul vascular cerebral sau atacul ischemic tranzitoriu în antecedente. Tratamentul trombozei venoase profunde (TVP) și al emboliei pulmonare (EP) și prevenirea recurenței TVP și a EP la adulți. *Copii și adolescenți:* Tratamentul tromboembolismului venoase (TEV) și prevenirea recurenței TEV la copii și adolescenți cu vârsta mai mică de 18 ani și cu greutatea peste 50 kg după cel puțin 5 zile de la tratamentul anticoagulant parenteral inițial. **Contraindicații:** KARDATUXAN 2,5 mg, 10 mg, 15 mg, 20 mg: Hipersensibilitate la substanța activă sau la oricare dintre excipienți; Hemoragie activă, semnificativă din punct de vedere clinic; Leziune sau afecțiune considerată a prezenta un risc semnificativ de sângerare majoră. Aceasta poate include ulcerația gastrointestinală curentă sau recentă, prezența neoplasmelor maligne cu risc crescut de sângerare, leziune recentă la nivelul creierului sau măduvei spinării, intervenție chirurgicală recentă cerebrală, spinală sau oftalmică, hemoragie intracraniană recentă, varice esofagiene cunoscute sau suspectate, malformații arterio-venoase, anevrism vascular sau anormalități vasculare intraspinale sau intracerebrale majore;Tratament concomitent cu orice alte anticoagulante, de exemplu, heparină nefracționată, heparină cu greutate moleculară mică (enoxaparina, dalteparina, etc.), derivate de heparină (fondaparina, etc.), anticoagulante orale (warfarina, dabigatran etexilat, apixaban etc.) exceptând situațiile specifice de schimbare a tratamentului anticoagulant sau când heparina nefracționată este administrată la dozele necesare pentru a menține deschis un cateter venos central sau arterial; Tratament concomitent al SCA cu terapie antiplachetară la pacienții cu accident vascular cerebral anterior sau accident ischemic tranzitoriu (AIT); Tratament concomitent al BAC/BAP cu AAS la pacienții cu accident vascular hemoragic sau lacunar în antecedente sau cu orice accident vascular cerebral în interval de o lună; Afecțiune hepatică asociată cu coagulopatie și risc hemoragic relevant din punct de vedere clinic, incluzând pacienții cu ciroză clasele B și C ale sistemului de clasificare Child Pugh; Sarcina și alăptarea.**Atenționări și precauții speciale pentru utilizare:** KARDATUXAN 2,5 mg: La pacienții cu SCA, eficacitatea și siguranța rivaroxaban 2,5 mg de două ori pe zi au fost investigate în administrare concomitentă cu medicamentele antiplachetare AAS în monoterapie sau AAS plus clopidogrel/ticlopidină.La pacienții cu BAC/BAP cu risc crescut de evenimente ischemice, eficacitatea și siguranța rivaroxaban 2,5 mg de două ori pe zi au fost investigate în asociere cu AAS. La pacienți după procedura recentă de revascularizare a membrului inferior din cauza BAP simptomatice, eficacitatea și siguranța rivaroxaban 2,5 mg de două ori pe zi au fost investigate în asociere cu medicamentul antiplachetar AAS în monoterapie sau AAS plus clopidogrel pe termen scurt. Dacă este necesar, tratamentul combinat antiplachetar cu clopidogrel trebuie să fie de scurtă durată; tratamentul combinat antiplachetar pe termen lung trebuie evitat. KARDATUXAN 10 mg, 15 mg, 20 mg: Se recomandă supravegherea din punct de vedere clinic pe toată durata perioadei de tratament. Risc hemoragic: pacienții trebuie monitorizați cu atenție pentru semnele de sângerare. Se recomandă să fie utilizat cu precauție în condiții cu risc crescut de hemoragie. Administrarea Kardatuxan trebuie întreruptă dacă apare hemoragie severă. Alți factori de risc hemoragic: rivaroxaban nu este recomandat la pacienți cu risc crescut de sângerare. Pacienți cu proteze valvulare:Rivaroxaban nu trebuie utilizat pentru tromboprofilaxie la pacienții care au trecut recent printr-o înlocuire percutanată de valvă aortică (TAVI).Pacienți cu sindrom antifosfolipidic: Rivaroxaban nu sunt recomandate la pacienții cu antecedente de tromboză, care sunt diagnosticați cu sindrom antifosfolipidic.Pacienții cu EP instabili hemodinamic sau pacienții care necesită tromboliză sau embolectomie pulmonară: Kardatuxan nu este recomandat ca alternativă la heparina nefracționată la pacienții cu embolie pulmonară care sunt instabili hemodinamic sau care pot beneficia de tromboliză sau embolectomie pulmonară, deoarece siguranța și eficacitatea rivaroxaban nu au fost stabilite în aceste situații clinice. KARDATUXAN 10 mg: Recomandări privind dozele înainte și după proceduri invazive și intervenții chirurgicale, altele decât intervențiile chirurgicale elective pentru substituția șoldului sau a genunchiului: Dacă este necesară o procedură invazivă sau o intervenție chirurgicală, trebuie oprită administrarea Kardatuxan 10 mg cu cel puțin 24 ore înainte de intervenție, dacă este posibil, precum și în funcție de opinia clinică a medicului. Dacă procedura nu poate fi amânată, trebuie evaluat riscul de sângerare comparativ cu gradul de urgență al intervenției. KARDATUXAN 15 mg, 20 mg: Recomandări privind dozele înainte și după proceduri invazive și intervenții chirurgicale: Dacă este necesară o procedură invazivă sau o intervenție chirurgicală, trebuie oprită administrarea Kardatuxan 15 mg sau Kardatuxan 20 mg cu cel puțin 24 ore înainte de intervenție, dacă este posibil, precum și în funcție de opinia clinică a medicului. Dacă procedura nu poate fi amânată, trebuie evaluat riscul de sângerare comparativ cu gradul de urgență al intervenției. **Reacții adverse:** KARDATUXAN 2,5 mg, 10 mg, 15 mg, 20 mg: Reacțiile adverse raportate cel mai frecvent la pacienții la care se administrează rivaroxaban au fost hemoragiile. Hemoragiile raportate cel mai frecvent au fost epistaxisul (4,5%) și hemoragia de tract gastrointestinal (3,8%). Frecvente (≥1/100 și <1/10): Anemie (inclusiv parametri de laborator corespunzători); Amețeli, cefalee; Hemoragie oculară (inclusiv hemoragie conjunctivală); Hipotensiune arterială, hematom; Epistaxis, hemoptizie; Sângerare gingivală, hemoragie la nivelul tractului gastrointestinal (inclusiv hemoragie rectală), dureri gastrointestinale și abdominale, dispepsie, greață, constipație, diaree, vărsături; Creștere a valorilor serice ale transaminazelor; Prurit (inclusiv cazuri mai puțin frecvente de prurit generalizat), erupție cutanată tranzitorie, echimoză, hemoragie cutanată și subcutanată; Dureri la nivelul extremităților; Hemoragie la nivelul tractului urogenital (inclusiv hematurie și menoragie), insuficiență renală (inclusiv creșterea creatininei serice, creșterea ureei serice); Febră, edem periferic, scădere a tonusului general și a energiei (inclusiv fatigabilitate și astenie); Hemoragie după o procedură (inclusiv anemie postoperatorie și hemoragie la nivelul plăgii), contuzie, secreții la nivelul plăgii. **Data și numărul autorizației de punere pe piață:** 2,5 mg - Nr.29430; 10 mg –Nr. 29431; 15 mg – Nr.29432; 20 mg – Nr.29433 din 30.11.2023. **Statutul legal:** cu prescripție medicală. **Data revizuirii textului:** Aprilie 2024. *Acest material publicitar este destinat persoanelor calificate să prescrie, să distribuie și/sau să elibereze medicamente. Pentru informații complete vă rugăm să consultați rezumatul caracteristicilor produsului. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției Medicamentului și Dispozitivelor Medicale (AMDM) http://nomenclator.amdm.gov.md/*

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