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ЗМІСТ / CONTENTS

Н. Войтюк
Критерії вибору сітчастого імплантату
у лапароскопічній герніопластиці Transabdominal Preperitoneal Patch 8
N. Voytyuk
Criteria for choosing a mesh implant
in laparoscopic Transabdominal Preperitoneal Patch hernioplasty 8

Н. Друцул-Мельник, Л. Іванова
Оцінка ризиків розвитку емоційного вигорання
в медичних сестер педіатричних відділень в період пандемії COVID-19 17
N. Drutsul-Melnyk, L. Ivanova
Risk assessment of emotional burnout development among paediatric ward nurses
during the COVID-19 pandemic 17

С. Куріакос, Н. АК, С. Реванкар, Б. Шетті, С. Шетті
Морфологія, пневматизація, септація, виступ сусідніх структур
у клиноподібну пазуху – ретроспективне радіологічне дослідження 25
S. Kuriakose, N. AK, S.r Revankar, B. Shetty, S. Shetty
Morphology, pneumatization, septation, and protrusion
of nearby structures into the sphenoid sinus: A retrospective radiological study 25

О. Кущ, А. Пайдаркіна
Дослідження антигенпрезентуючих клітин в брижі кишки в нормі і при спайковому процесі 32
O. Kushch, A. Paidarkina
Investigation of antigen-presenting cells in the intestinal mesentery in normal and adhesive processes 32

С. Мостовий
Взаємозв'язок показників плазмового гемостазу та варіабельності серцевого ритму
у хворих на хронічний коронарний синдром у поєднанні COVID-19 40
S. Mostovyi
Interrelation of plasma haemostasis and heart rate variability in patients
with chronic coronary syndrome in combination with COVID-19 40

О. Олійник
Ефективність тромболітичної терапії у хворих на COVID-19 важкого перебігу
та тромбоемболію легеневої артерії 50
O. Oliinyk
Effectiveness of thrombolytic therapy in patients with severe COVID-19
and pulmonary embolism 50

Л. Посоленик
Структурно-функціональна реорганізація слинних залоз при онкопатології: міні огляд 60
L. Posolenyk
Functional-structural reorganisation of salivary glands in oncological pathology: A mini-review 60

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Criteria for choosing a mesh implant in laparoscopic Transabdominal Preperitoneal Patch hernioplasty

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Abstract. Laparoscopic Transabdominal Preperitoneal Patch hernioplasty is an important method of treating inguinal hernias, but the lack of data on the comparative effectiveness of anatomical 3D mesh and traditional flat mesh makes it difficult to choose the optimal implant to reduce the risk of recurrence and complications. The aim of the study was to compare the effectiveness of anatomical 3D mesh and traditional flat mesh in laparoscopic hernioplasty with Transabdominal Preperitoneal Patch, as well as to determine the key criteria for implant selection. The objectives of the study were to analyse the recurrence rate, duration of surgery, postoperative pain, complication rate and patient satisfaction in the two groups. The study included 187 patients who were divided into two groups: 92 patients received traditional flat meshes and 95 patients received 3D anatomical meshes. Data were collected over 18 months and analysed using statistical methods. The use of anatomical 3D meshes reduced the time of surgery. The average level of postoperative pain according to the Visual Analogue Scale in the group with anatomical meshes was 30% lower. The complication rate in the anatomical mesh group was 5%, while in the flat mesh group it was 12%. Patient satisfaction in the group with anatomical 3D meshes was significantly higher. The results of the study confirm the advantage of anatomical 3D mesh in laparoscopic hernioplasty with Transabdominal Preperitoneal Patch, which reduces the time of surgery, reduces the incidence of recurrence, postoperative pain and complications, and increases patient satisfaction

Keywords: inguinal hernia; three-dimensional materials; postoperative discomfort; complications; effectiveness; comparative review

INTRODUCTION

Laparoscopic Transabdominal Preperitoneal Patch (TAPP) hernioplasty, despite its popularity due to its minimally invasive approach that reduces the risk of recurrence and speeds up recovery, remains a subject of debate as its effectiveness requires further research, especially regarding the optimal choice of mesh implant to minimise complications. Anatomical 3D meshes offer an innovative approach that can improve surgical outcomes due to their ability to better adapt to patient anatomy, reduce postoperative pain, reduce complications and speed recovery, although their effectiveness compared to traditional flat meshes remains to be seen; individualised implant selection remains key to accommodate unique patient anatomy. However, to confirm these findings, large-scale clinical trials are needed to compare the long-term results of using 3D anatomical meshes with traditional methods. It is also relevant to investigate the impact of different types of mesh on postoperative pain and quality of life in the long term after surgery. Only after obtaining more detailed data, will it be possible to definitively state the advantages of a particular type of mesh implant. So, although laparoscopic TAPP hernioplasty shows encouraging results, it needs further study to definitively confirm its effectiveness and safety. It is also important to continue research into the development of new implant materials and fixation techniques, which will improve the quality of inguinal hernia treatment and patient outcomes.

The study conducted by V. Hrubnik *et al.* [1] emphasises the key role of the choice of surgical method in the treatment of recurrent inguinal hernias, highlighting the significant advantages of laparoscopic techniques, including shorter surgery time, reduced risk of complications,

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postoperative pain and faster recovery of patients compared to traditional open surgery. Less traumatic than open surgery, laparoscopic hernioplasty is particularly suitable for patients with previous surgeries where scar tissue is difficult and provides reliable hernia repair, reducing the risk of recurrence; however, further research remains to compare the early and long-term outcomes of laparoscopic and open surgery, including technical aspects, pain levels, recovery rates and recurrence rates.

The results of the work by A. Bilay [2] confirmed the high effectiveness of laparoscopic TAPP hernioplasty in patients with primary and recurrent inguinal hernias, especially due to the use of modern anatomical 3D meshes that reduce the risk of complications and shorten recovery time. A study of the modified technique showed that the improved technique significantly reduces the operation time, reduces the recurrence rate due to a more secure mesh implant fixation, and reduces postoperative complications such as seromas, haematomas, infections, and pain, facilitating faster recovery and increasing patient satisfaction with treatment results.

I. Babiy [3] conducted a study on the comparative evaluation of various alloplastic methods of surgical treatment of inguinal hernia. The purpose of the study was to determine the most effective approaches to alloplasty in the treatment of inguinal hernias, ensuring a minimum recurrence rate, low postoperative complications and high quality of life for patients. The results have shown that the use of modern mesh implants with different fixation methods significantly affects the success of the surgical intervention. In particular, self-fixing meshes reduce the risk of seromas and infections, while lightweight polypropylene materials are better at reducing chronic pain and shortening recovery time. 3D anatomical meshes have been shown to significantly reduce the risk of hernia recurrence compared to flat meshes, increasing the long-term effectiveness of operations and reducing the need for repeat interventions. The study by the researcher confirmed that the choice of alloplasty method and type of mesh implant has a decisive impact on the success of treatment, reducing complications and improving the quality of life of patients in the postoperative period.

The scientific work of Q. Saiding *et al.* [4] showed that a properly selected mesh implant, especially an anatomical 3D mesh, can minimise postoperative pain and improve overall patient satisfaction with the results of surgery. This is especially important for patients at increased risk of complications, such as the elderly or patients with chronic diseases. The relevance of this approach is also confirmed by M. Meng *et al*. [5] and Y. Wu *et al.* [6], who demonstrate the benefits of 3D anatomical meshes in the long term, including a reduced risk of recurrence and improved quality of life.

Analysis of the researches of N. Thanh Xuan & N. Huu Son [7], S. Savoliuk *et al.* [8] confirms the feasibility of using anatomical 3D meshes in laparoscopic TAPP hernioplasty to reduce the recurrence rate and improve the postoperative period. Further improvement of inguinal hernia treatment methods based on these data will contribute to improving the quality of medical care. However, despite the benefits of 3D anatomical mesh, its use remains a matter of debate, and more research is needed to accurately assess its effectiveness compared to traditional flat mesh, with particular attention to recurrence rates, postoperative pain, complications, and patient satisfaction.

The study was focused on analysing the main factors in choosing a mesh implant for laparoscopic inguinal hernia surgery. The research paper pays special attention to the comparison of traditional flat meshes and anatomical 3D meshes in terms of their effectiveness, impact on postoperative recovery and long-term results.

MATERIALS AND METHODS

The study was conducted at one of the leading medical Kyiv surgery centres specializing in hernia surgery – Kyiv City Clinical Hospital No. 1 – for 18 months from 09.2021 to 03.24. The study involved 187 patients with a confirmed diagnosis of inguinal hernia who were undergoing elective laparoscopic hernioplasty using the TAPP method. All patients who participated in the study provided informed consent to participate in the study and to use their data for scientific purposes. The first group (group A (92 patients)) received traditional flat meshes that are widely used in surgical practice. The second group (group B (95 patients)) received 3D anatomical meshes with a more complex structure designed to better fit the patient's anatomical structures. All surgeries were performed under general anaesthesia according to standard surgical protocols.

All participants were informed of the study objectives, methods, possible risks and benefits before the study began. Participants were ensured the right to voluntary participation and could refuse to participate or withdraw from the study at any stage without negative consequences. Informed consent was obtained from all participants, and the process of obtaining it complied with the principles of confidentiality and personal data protection. The study was also approved by the relevant ethics committee at the institution where it was conducted, which ensures that all ethical standards were met. The study reports, data collected and analysed were conducted with due regard for the confidentiality of participants, in accordance with applicable national and international regulations, such as the World Medical Association Declaration of Helsinki [9], Law of Ukraine No. 2297-VI "On Personal Data Protection" [10]. These ethical standards ensure proper protection of the rights and interests of research participants and guarantee compliance with high standards of research practice.

Patients had to be 18 years of age or older and could be either male or female. Surgery was indicated in cases of primary inguinal hernia. At the same time, patients had to have no serious comorbidities that could affect the results of the study. Patients with congenital or severe comorbidities, such as cancer, diabetes mellitus in the stage of decompensation, severe cardiovascular disease or blood clotting disorders, were excluded from the study. All surgeries were performed by the same team of surgeons to ensure standardization of surgical procedures and minimise variations that could affect the results. The TAPP technique was used, which involves accessing the hernia sac through the preperitoneal space and then placing a mesh implant. In group A, the traditional flat mesh was used, which was fixed with a geonio-stapler. In group B, anatomical 3D meshes were used, which, due to their shape, provided a tighter fit to the anatomical structures and did not require fixation.

The study lasted for 18 months, during which the following key parameters were evaluated: duration of surgery, recurrence rate, postoperative pain, complication rate and patient satisfaction. The duration of the operation was recorded for each patient, from the first incision to the last suture. The hernia recurrence rate was determined based on regular patient examinations every three months for a year, which included clinical examination and ultrasound. The level of postoperative pain was assessed using a visual analogue scale (VAS) on the first, third, seventh and thirtieth day after surgery, where patients rated pain on a scale from 0 (no pain) to 10 (unbearable pain). The incidence of complications such as seroma, haematoma, infection or chronic pain was carefully documented and classified as early (up to 30 days postoperatively) and late (more than 30 days postoperatively). Patient satisfaction was assessed through questionnaires administered 3 and 6 months after surgery, where patients rated their satisfaction with the results on a scale from 1 (completely dissatisfied) to 5 (completely satisfied). Data were also collected using a standardised questionnaire administered at two time points: 3 months and 6 months after surgery. The questionnaire included questions aimed at assessing patient satisfaction based on several criteria, such as quality of life after surgery, presence, or absence of postoperative complications, postoperative pain, and overall sense of treatment success. Patients were asked to rate their satisfaction on a five-point scale, with 1 indicating complete dissatisfaction and 5 indicating complete satisfaction with the results. To assess satisfaction, a scale was used that allowed patients to rate different aspects of treatment. For example, patients rated their physical activity after surgery, discomfort or pain, and the overall impact of the surgery on their daily lives. In addition, the questionnaire included questions about postoperative complications, such as infections, seromas, haematomas and chronic pain, which allowed for a comprehensive assessment of the effectiveness of the surgery.

The data analysis procedure included processing the results of the questionnaire to determine the mean values of patient satisfaction scores, complication rates, and postoperative pain levels. The data were analysed using appropriate statistical methods to determine significant differences between patient groups. The analysis also included a comparison of results at different time points to identify the dynamics of patient satisfaction during the follow-up period. All data were systematised and used to draw conclusions about the effectiveness of the surgical interventions and their impact on the quality of life of patients. The collected data were subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS) software. The t-test for independent samples and the χ^2-test for categorical variables were used to compare the two groups for each of the parameters. The level of significance was set at 0.05. Data were presented as means (M) and standard deviations (SD) for quantitative indicators, and as percentages for qualitative indicators.

The results of the study were presented in the form of tables and graphs, which allowed us to visually compare the effectiveness of traditional flat meshes and anatomical 3D meshes in laparoscopic TAPP hernioplasty. Particular attention was paid to the recurrence rate, postoperative pain level and overall patient satisfaction, as these indicators are critical for assessing the long-term effectiveness of the operation.

RESULTS

The selection of the appropriate mesh implant and the correct placement technique are critical to the success of TAPP hernioplasty surgery. It is crucial that surgeons have all the necessary skills and knowledge to make optimal use of these materials to achieve the best clinical results. Different types of mesh implants have a significant impact on the course of surgery and the postoperative period. The study covered several key parameters, such as the duration of surgery, recurrence rate, postoperative pain level, complication rate and patient satisfaction. These parameters are critical for assessing the long-term effectiveness and safety of mesh implant surgery.

One of the key parameters that was carefully evaluated in this study was the duration of the surgery. According to the results obtained, the use of anatomical 3D meshes has significantly reduced the operation time. Reducing the duration of the operation is directly related to a number of important factors: reduced risk for the patient, reduced time under anaesthesia, and, as a result, reduced likelihood of postoperative complications. In addition, the use of 3D anatomical meshes contributed to a more accurate and faster implant fixation due to their optimal conformity to the patient's anatomical features. This allowed surgeons to perform fewer manipulations during mesh placement, which not only reduced the time of surgery but also reduced the trauma of the procedure for the patient. Thus, as shown in Table 1, the study demonstrates the importance of using 3D anatomical mesh in laparoscopic TAPP hernioplasty, emphasizing its ability to improve surgical outcomes and patient safety.

Table 1. Duration of surgery

Research team	Type of hernia defect	Number of patients	Mean value of the duration of surgery (in min), X ± m
Control group (simple grid)	Lateral (oblique)	48	74.5 ± 0.8
	Medial (straight)	41	65.6 ± 0.5
	Femoral	3	67.7 ± 1.5
Main group (3D grid)	Lateral (oblique)	43	47.7 ± 0.4
	Medial (straight)	47	38.3 ± 0.6
	Femoral	5	32.4 ± 1.1

Source: compiled by the author

One of the key indicators of the effectiveness of hernioplasty is the recurrence rate, which directly affects the long-term success of treatment. According to the results of an 18-month follow-up, the recurrence rate among patients implanted with traditional flat mesh was 8%, while in the group of patients who received anatomical 3D mesh, this figure was only 2%. These data indicate a significant advantage of anatomical 3D mesh in preventing hernia recurrence. The main factor behind this advantage is the ability of 3D anatomical meshes to optimally adapt to the individual anatomical features of the patient. Due to their three-dimensional structure, such meshes provide a more precise fit to the tissues, which creates a more stable and secure implant fixation. In contrast, traditional flat meshes often do not take into account individual anatomical features, which can lead to their displacement and, as a result, to an increased risk of hernia recurrence. Thus, the use of 3D anatomical mesh in hernioplasty seems to be a more effective approach that helps to reduce the recurrence rate and improve the quality of life of patients after surgery. These results emphasise the importance of an individualised approach to implant selection based on a detailed consideration of the patient's anatomical characteristics, which is key to successful hernia repair and is presented in Table 2.

Table 2. Relapse rates in groups with different types of mesh

Mesh type	Relapse rate, %
Traditional flat meshes	8
Anatomical 3D meshes	2

Source: compiled by the author

One of the key aspects that was thoroughly analysed in the study was postoperative pain in patients who underwent mesh implantation during TAPP laparoscopic hernioplasty. The results of the study show a significant reduction in postoperative pain in patients who underwent implantation of anatomical 3D mesh compared to those who underwent traditional flat mesh. In particular, the average pain level in patients who received anatomical 3D meshes was 3.5 points on the VAS (Visual Analogue Scale), which is significantly lower by 30% compared to 5.0 points in the group with traditional flat meshes. This reduction in postoperative pain is attributed to the improved adaptation of 3D anatomical meshes to individual patient anatomical structures. Due to their three-dimensional shape, these meshes fit better to the tissues, minimizing pressure on the surrounding structures, which significantly reduces the risk of inflammation and discomfort. This adaptation not only helps to reduce patient pain, but also speeds up the recovery process by reducing the need for painkillers after surgery. These results highlight the importance of choosing the right type of mesh implant to optimise postoperative recovery, which is key to improving patients' quality of life in the postoperative period (Table 3).

Table 3. Postoperative pain according to the VAS scale

Mesh type	Average pain level, points
Traditional flat meshes	5
Anatomical 3D meshes	3.5

Source: compiled by the author

The study thoroughly evaluated the incidence of postoperative complications that occur after laparoscopic hernioplasty using different types of mesh implants. The results showed that the overall complication rate in patients who had 3D anatomical mesh implants was 5%. This is significantly lower than in patients who received traditional flat meshes, where the complication rate reached 12%. The most common postoperative complications were seroma, haematoma, infection, and chronic pain. The decrease in the complication rate in patients who received 3D anatomical mesh can be explained by several factors. Firstly, due to their three-dimensional structure, these meshes integrate better with the surrounding tissues, which ensures their stable fixation and reduces the risk of implant displacement or deformation. This, in turn, reduces the risk of developing infectious complications, as the implant remains in a stable position and does not create conditions for fluid accumulation or seroma formation. Secondly, better adaptation of 3D meshes to the patient's anatomy helps to reduce postoperative pain, as it reduces pressure on the surrounding tissues and nerve endings. These results highlight the advantages of using anatomical 3D meshes compared to traditional flat meshes, which significantly reduce the risk of postoperative complications. This, in turn, improves overall treatment outcomes and increases the quality of life of patients in the postoperative period.

The level of patient satisfaction is one of the key indicators of the success of a surgical intervention, as it reflects not only the technical efficiency of the operation, but also the quality of life of patients after treatment. The post-operative survey found that patients who received anatomical 3D mesh implants demonstrated a significantly higher level of satisfaction with the results of the surgery compared to those who received traditional flat mesh. Specifically, 95% of patients in the anatomical 3D mesh group expressed full or partial satisfaction, while the figure for the flat mesh group was only 80%. Patients who received anatomical 3D meshes reported a significantly higher level of comfort after surgery, which is explained by the more natural fit of the meshes to the tissues and the absence of a foreign body sensation that often occurs when using flat meshes. This, in turn, had a positive impact on their quality of life in the postoperative period. In addition, patients who received 3D

anatomical mesh had a lower incidence of complications and reduced postoperative pain, which also contributed to their high level of satisfaction. Thus, the results of the study shown in Table 4 demonstrate the superiority of 3D anatomical meshes over traditional flat meshes in terms of patient experience and overall surgical success.

Table 4. Level of patient satisfaction

Mesh type	Full satisfaction, %	Partial satisfaction, %
Traditional flat meshes	70	10
Anatomical 3D meshes	85	10

Source: compiled by the author

The results of this study clearly demonstrate the advantages of using anatomical 3D meshes compared to traditional flat meshes in laparoscopic hernioplasty using the TAPP technique. All key indicators – from the duration of the operation to the level of patient satisfaction – indicate that 3D anatomical mesh is more effective and safer for patients. A 10-minute reduction in surgery time can have a significant impact on reducing surgical risks and improving outcomes. The lower recurrence rate (2% vs. 8%) is a testament to the more stable anchoring of 3D anatomical meshes and their ability to better conform to the patient's anatomy. A 30% reduction in postoperative pain makes the rehabilitation period less stressful for patients and reduces the need for painkillers. In addition, a significantly lower incidence of postoperative complications (5% vs. 12%) underscores the advantage of 3D anatomical meshes in preventing serious problems after surgery. The high level of patient satisfaction (95% vs. 80%) indicates that 3D anatomical mesh not only improves clinical outcomes, but also improves the quality of life of patients after surgery.

Thus, the results of the study confirm the feasibility of using anatomical 3D meshes in laparoscopic hernioplasty using the TAPP method, making them the best choice for surgeons and patients. The study showed that the use of 3D anatomical mesh in TAPP laparoscopic hernioplasty is more effective than traditional flat mesh in a number of key ways. Reduced surgery time and reduced recurrence rates confirm that anatomical meshes provide better adherence to the tissues and minimal trauma during surgery. The reduction in postoperative pain and complications is also a strong argument in favour of 3D anatomical meshes, which increase overall patient satisfaction with the results of surgery.

DISCUSSION

In a study that focused on the use of 3D anatomical mesh in laparoscopic TAPP hernioplasty, several important benefits of these implants were identified. In particular, 3D meshes resulted in shorter operative times, lower recurrence rates, reduced postoperative pain, and increased patient satisfaction. These results differ from those obtained in studies of traditional flat meshes, which allows for a detailed comparison. For example, a study by C.S. Seefeldt *et al.* [11] showed that biological meshes have a lower risk of chronic pain, but at the same time demonstrate a higher recurrence rate compared to synthetic meshes. In this study, anatomical 3D meshes showed both a low level of postoperative pain and a significantly lower recurrence rate (only 2%). This indicates that anatomical 3D meshes may be more effective in ensuring long-term implant stability than biological meshes, while reducing the risk of chronic pain.

Another scientific work by J.F. FitzGerald & A.S. Kumar [12] also notes that biological meshes have a higher risk of recurrence, but better biocompatibility and a lower risk of chronic pain compared to synthetic meshes. In our study, anatomical 3D meshes, although synthetic, demonstrate excellent results in both of these aspects: they provide a low recurrence rate and reduce postoperative pain. This indicates that properly selected and structured synthetic meshes, such as 3D anatomical meshes, can provide benefits that exceed both biological and traditional synthetic meshes. Thus, the results of the study highlight that 3D anatomical mesh may be the best choice for patients who need not only pain relief but also a reliable, long-term solution for hernia repair. This distinguishes them from biological meshes, which, while offering a high level of biocompatibility and a lower risk of chronic pain, have an increased risk of recurrence, which can be a critical factor in choosing a treatment method. The results of the study, which focused on the use of 3D anatomical meshes in TAPP laparoscopic hernioplasty, showed significant advantages of these implants in terms of operative time, recurrence rate and postoperative pain. These indicators are also related to the methods of mesh fixation, which is confirmed by the study by Q. Saiding *et al.* [4], which showed that the method of mesh fixation significantly affects the recurrence rate, with adhesive and self-adhesive meshes showing better results. This study, which focused on anatomical 3D meshes, confirms this conclusion. The use of anatomical 3D meshes, which provide better conformity to anatomical structures and natural self-locking, led to a reduction in the recurrence rate of up to 2%. This confirms the effectiveness of self-locking meshes and emphasises the importance of choosing the right fixation method.

A. Jangjoo *et al.* [13] noted that the wrong choice of mesh size and shape, as well as inadequate fixation, are key risk factors for mesh migration. The results of the study showed a low complication rate and no cases of implant migration when using anatomical 3D meshes, pointing out the importance of choosing the right size and shape of the mesh, as well as proper fixation to prevent migration. M. Matikainen *et al.* [14] found that the choice of mesh and the method of fixation affect the incidence of chronic pain after surgery. In our study, 3D anatomical meshes showed a significant reduction in postoperative pain, which may also be the result of effective mesh fixation. This confirms the importance of selecting fixation methods that minimise chronic pain and improve overall surgical outcomes [15, 16]. Thus, this study complements and confirms the findings of other studies, demonstrating that the correct choice of anatomical 3D mesh and appropriate fixation methods are

critical to reduce the incidence of recurrence, implant migration, and postoperative pain, which generally improves the results of laparoscopic TAPP hernioplasty. The results of this study, which compared the effectiveness of 3D anatomical mesh in laparoscopic TAPP hernioplasty with traditional flat mesh, are largely consistent with the findings of other studies looking at new materials and mesh coatings.

O.A. Olanrewaju *et al.* [17] emphasised the importance of choosing a mesh based on the patient's anatomy and the type of hernia. The study showed that the use of anatomical 3D meshes that better match the patient's anatomy reduces the time of surgery and the incidence of recurrence. This confirms that taking into account anatomical features is a key factor in choosing a mesh implant. S. Elango *et al.* [18] point out the importance of using lightweight and biocompatible materials to reduce the risk of chronic pain. In the study, anatomical 3D meshes demonstrated a reduction in postoperative pain, which is consistent with recommendations for choosing lightweight materials that reduce pressure on surrounding tissues and reduce chronic pain.

R. Bittner *et al.* [19], A.L. Vorst *et al*. [20] and K.Y. Wu *et al.* [21] noted that coated mesh reduces the incidence of postoperative complications such as infections compared to uncoated mesh. Although the study did not include a comparison of coated and uncoated meshes, the reduced complication rate with 3D anatomical meshes may be partly due to their design, which allows for better adaptation to the tissues and reduces the risk of infectious complications. Polypropylene meshes have better results in reducing recurrence and chronic pain compared to polyester meshes. The results of the study support these findings, as anatomical 3D meshes, which are predominantly made of polypropylene, provided a significant reduction in recurrence and postoperative pain compared to flat meshes. Thus, this study confirms the importance of mesh materials and coatings in achieving optimal results in laparoscopic TAPP hernioplasty. Due to their design and material, 3D anatomical meshes demonstrate significant benefits in reducing operative time, recurrence rates, postoperative pain, and complications, which is consistent with the findings of other researchers in this field. In this study, 3D anatomical meshes demonstrated significant benefits over traditional flat meshes, which is reflected in reduced operative time, reduced recurrence rates, reduced postoperative pain, and increased patient satisfaction. These results provide an interesting comparison with studies evaluating the effectiveness of lightweight polypropylene mesh.

Studies by J. Li *et al.* [22], P. Prakash *et al*. [23] and A. Currie *et al.* [24] found that the use of heavy meshes led to an increase in the incidence of chronic pain and complications compared to lightweight polypropylene meshes. In comparison to the study, anatomical 3D meshes, although not directly compared to heavy meshes, also showed a reduction in postoperative pain, which may indicate similar benefits associated with the lightness and anatomical conformity of these meshes. In addition, the results of a study by foreign scientists indicate that lightweight polypropylene mesh showed better results in reducing chronic pain and faster recovery of patients compared to heavy mesh. This is in line with the findings of M. Melkemichel *et al.* [25] and C.D. Deveci *et al.* [26], where anatomical 3D meshes provided pain reduction and improved patient comfort, which is likely due to their optimal structure and lightness. Lightweight polypropylene meshes provide better results in elderly patients, reducing the incidence of chronic pain and accelerating recovery. The study did not separately analyse the age of the patients, but the overall reduction in postoperative pain and improved outcomes observed may also be relevant for older patients.

K.F. Pedersen *et al.* [27] emphasised that lightweight mesh reduces the risk of chronic pain and improves long-term outcomes after surgery. This conclusion coincides with the data obtained by B. Shiroud Heidari *et al.* [28], where the use of anatomical 3D meshes helped to reduce chronic pain and increase overall patient satisfaction with the results of surgery. Thus, although the study focused on comparing 3D anatomical meshes with traditional flat meshes, the results are consistent with the benefits of lightweight polypropylene mesh described in the literature. This indicates that the lightness and conformity of the mesh to the patient's anatomy are critical factors affecting the success of laparoscopic hernioplasty.

The use of three-dimensional self-locking meshes significantly reduced the operation time and reduced the recurrence rate compared to lightweight polypropylene meshes [29]. The study also confirms this, as the average duration of surgery for anatomical 3D mesh was 10 minutes shorter than for flat mesh, and the recurrence rate was reduced to 2%. The studies by K. Baylón *et al.* [30] and A. Robbins *et al.* [31] emphasise the reduction in the duration of surgery and the incidence of complications when using self-locking mesh. In the study, the complication rate in the group with anatomical 3D meshes was 5%, while in the group with flat meshes, it was 12%, which confirms the advantages of three-dimensional meshes. Three-dimensional mesh provides better stability and a lower risk of recurrence in the long term. The study confirmed these findings, demonstrating that anatomical 3D meshes adhere better to the tissues, reducing the risk of implant displacement.

In the study, patients with anatomical 3D meshes reported a 30% reduction in VAS pain compared to flat meshes, which is confirmed by the data of other scientists M. Schulze *et al*. [32] and G. Natale *et al.* [33], who found that three-dimensional meshes provide better stability and a lower risk of implant displacement. The use of self-locking meshes reduces the time of surgery and reduces the risk of recurrence, especially in patients at high risk of complications. The study also showed a reduction in the recurrence rate of up to 2% in the group with 3D meshes, which confirms these findings. Research by Ukrainian and foreign scientists confirms the importance of choosing the right mesh implant in TAPP laparoscopic hernioplasty, emphasizing the benefits of three-dimensional, lightweight and biocompatible mesh in reducing the risk of complications, recurrence and increasing patient satisfaction.

CONCLUSIONS

Laparoscopic TAPP hernioplasty is one of the most effective treatments for inguinal hernias, where the choice of mesh implant plays a key role in reducing the risk of recurrence and complications. The study results clearly demonstrated the significant advantages of 3D anatomical mesh. In particular, the use of such meshes has significantly reduced the operation time, which is an important factor in

surgical practice. In addition, patients who had 3D anatomical meshes implanted had a lower level of postoperative pain, which was confirmed by the VAS scale. The incidence of postoperative complications, such as infections and seromas, was also significantly lower in the group with anatomical 3D meshes. Patients who had 3D anatomical mesh implanted demonstrated a significantly higher level of satisfaction with the results of the surgery, which is a critical indicator of the quality of medical services. The study also showed that the use of anatomical 3D meshes reduces the recurrence rate by ensuring better adhesion of the implant to the tissues and minimal trauma during surgery. The reduction in postoperative pain and complication rates are strong arguments in favour of 3D anatomical meshes, which increase the overall satisfaction of patients with the results of surgery.

It is worth noting that the duration of patient follow-up was relatively short, which limits the assessment of long-term outcomes and recurrence. In addition, the study did not take into account all possible factors that could affect the outcome of the surgery, such as individual anatomical differences and patient comorbidities. These limitations highlight the need for larger and longer studies to definitively determine the effectiveness of 3D anatomical mesh compared to traditional implants.

The data obtained can be used to improve surgical protocols, which will contribute to the improvement of the quality of medical services and raise the standards of surgical practice. The introduction of anatomical 3D meshes in TAPP laparoscopic hernioplasty can increase the effectiveness of inguinal hernia treatment, improving the quality of life of patients and reducing the risk of reoperation. Further studies should include larger patient samples and longer follow-up periods to determine the long-term effectiveness of 3D anatomical meshes. In addition, it is relevant to evaluate the cost-effectiveness of using such meshes in different clinical settings, which may help improve the standard of care for inguinal hernias.

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CONFLICT OF INTEREST

All author declares no conflict of interest in this article.

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Критерії вибору сітчастого імплантату у лапароскопічній герніопластиці Transabdominal Preperitoneal Patch

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Анотація. Лапароскопічна герніопластика Transabdominal Preperitoneal Patch є важливим методом лікування пахових гриж, але недостатність даних про порівняльну ефективність анатомічних 3D сіток і традиційних плоских сіток ускладнює вибір оптимального імплантату для зниження ризику рецидивів і ускладнень. Метою дослідження було порівняння ефективності анатомічних 3D сіток і традиційних плоских сіток у лапароскопічній герніопластиці Transabdominal Preperitoneal Patch, а також визначення ключових критеріїв для вибору імплантату. В задачі дослідження входило проаналізувати частоту рецидивів, тривалість операції, рівень післяопераційного болю, частоту ускладнень та задоволення пацієнтів у двох групах. Дослідження включало 187 пацієнтів, які були поділені на дві групи: 92 пацієнтів отримали традиційні плоскі сітки, і 95 пацієнтів – анатомічні 3D сітки. Дані збиралися протягом 18 місяців і аналізувалися статистичними методами. Використання анатомічних 3D сіток дозволило скоротити час операцій. Середній рівень післяопераційного болю за шкалою Visual Analog Scale у групі з анатомічними сітками був на 30 % нижчим. Частота ускладнень у групі з анатомічними сітками склала 5 %, у той час, як у групі з плоскими сітками цей показник був 12 %. Задоволення пацієнтів у групі з анатомічними 3D сітками було значно вищим. Результати дослідження підтверджують перевагу анатомічних 3D сіток у лапароскопічній герніопластиці Transabdominal Preperitoneal Patch, що забезпечує зменшення часу операції, зниження частоти рецидивів, післяопераційного болю і ускладнень, а також підвищення рівня задоволення пацієнтів

Ключові слова: пахові грижі; тривимірні матеріали; післяопераційний дискомфорт; ускладнення; результативність; порівняльний огляд

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Risk assessment of emotional burnout development among paediatric ward nurses during the COVID-19 pandemic

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Abstract. The issue of burnout among healthcare personnel is highly pertinent, particularly during the COVID-19 pandemic, which underlines the importance of this study. The research aimed to analyse the results of an anonymous survey conducted among paediatric ward nurses regarding burnout in the context of the COVID-19 pandemic, to optimise their work. The assessment of burnout levels was performed by analysing the results of an anonymous questionnaire (V. Boiko's questionnaire) completed by 135 nurses working in paediatric wards of different specialisations in healthcare facilities in Chernivtsi. Respondents were divided into two observation groups. Group I consisted of 83 nurses working in non-infectious paediatric wards, while 52 nurses from infectious paediatric wards were included in Group II. The average age of the nurses in Group I was 38.02 ± 0.9 years, while for Group II it was 43.81 ± 1.6 years ($p > 0.05$), and the length of service was 18.01 ± 0.9 and 22.09 ± 1.4 years, respectively ($p > 0.05$). It was found that among the surveyed respondents in Groups I and II, the burnout scores were significantly higher for nurses in non-infectious wards, particularly in the phases of "tension" (42 and 28.2 points, respectively, ($p < 0.05$), "resistance" (54.9 and 37.8 points, respectively, ($p < 0.05$), and "exhaustion" (40.7 and 26.2 points, respectively, ($p < 0.05$). The risk scores for the development of burnout phases (⩾37 points) among Group I nurses compared to Group II were as follows: "tension" phase: relative risk – 1.9, odds ratio – 4.2; "resistance" phase: relative risk – 1.9, odds ratio – 3.6; "exhaustion" phase: relative risk – 1.5, odds ratio – 2.7. It was established that during the COVID-19 pandemic, the chances of burnout registration among nurses in non-infectious wards increased by 2.7-4.2 times

Keywords: coronavirus infection; healthcare personnel; professional burnout; stress

INTRODUCTION

The relevance of the issue of emotional burnout is widely recognised, as burnout syndrome significantly impacts both individuals and society as a whole, transforming from a simple phenomenon into a syndrome characteristic of the modern world. Emotional burnout is associated with professions that involve constant interaction with people. Unlike stress, burnout is characterised by difficulties in adaptation due to prolonged exposure to stressors, and it manifests in a variety of clinical signs and symptoms [1].

I.H. Jonsdottir & A. Sjörs Dahlman [2] define emotional burnout as a "multidimensional construct" or a "syndrome consisting of an emotional component (depletion of emotional resources and decreased individual energy), depersonalisation (negative attitudes and feelings, lack of empathy), and reduced personal accomplishment (devaluation of personal achievements, negative self-evaluation of one's professional activities, and feelings of reduced competence)".

The World Health Organization (WHO) has recently included burnout syndrome in the 11th revision of the International Classification of Diseases as an occupational issue rather than a medical condition. Burnout is defined in the International Classification of Diseases (ICD-11) as

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a phenomenon resulting from chronic workplace stress that has not been successfully managed. The WHO guidelines [3] identify three key dimensions of occupational burnout: a) feelings of energy depletion and exhaustion; b) increased mental distance from one's job, negative or cynical attitudes related to one's job; and c) reduced professional effectiveness.

Burnout can affect workers in many professional fields and is prevalent in 13-27% of the working population. P. Galanis *et al.* [4] note that emotional burnout syndrome has been extensively studied in various sectors, particularly among teachers and healthcare professionals who have been most frequently affected.

Its high prevalence is attributed to both the frequent and successive systemic changes in healthcare and the specific nature of the profession. Other factors contributing to professional burnout include long working hours (12-24-hour shifts), holding a second job, frequent and repetitive interactions with certain patient groups (e.g., non-compliance, aggressive behaviour due to severe illness), constant increased responsibility, unstable working conditions, and the absence of organisational systems to recognise and reward the demonstrated effectiveness of nurses in the workplace [5-7].

Despite numerous studies demonstrating the negative impact of emotional burnout on healthcare workers [8, 9], there is currently a lack of well-developed strategies for addressing burnout and for early intervention in cases of anxiety and depression among healthcare professionals. This issue has become particularly pressing during major pandemics, such as the COVID-19 pandemic. The COVID-19 pandemic, as a model for large-scale pandemics, provides an ideal context for studying emotional burnout among healthcare workers, especially nurses, as the immense psychological burden and stressful working conditions significantly increase the likelihood of developing burnout. This study aimed to assess the severity of emotional burnout among paediatric nurses working in different departments during the COVID-19 pandemic, based on the analysis of results from an anonymous survey.

MATERIALS AND METHODS

A retrospective cohort study using simple random sampling was conducted between 2020 and 2021 to achieve the study's aim. An anonymous survey was administered to 135 paediatric nurses from various departments in healthcare facilities in Chernivtsi to diagnose the level of emotional burnout, utilising V. Boiko's questionnaire [10]. Respondents received the survey at their workplace, and the introductory section explained the purpose of the study, emphasised the anonymity of their participation, and assured them of data confidentiality. A note of gratitude for their participation was also included.

The questionnaire consisted of 84 questions and was divided into three sections. The first section focused on self-assessment of the "tension" phase, including levels of anxiety and depression, experiences of traumatic circumstances, and feelings of self-dissatisfaction. The second section evaluated "resistance", covering emotional-moral disorientation, inappropriate emotional responses, the expansion of emotional conservation, and the reduction of professional responsibilities. The third section assessed the "exhaustion" phase in nurses, focusing on emotional detachment, personal depersonalisation, emotional depletion, and psychosomatic and psychological disturbances of the vegetative nervous system.

The assessment method involved considering each of the 12 symptoms and calculating the total score for the three main phases of emotional burnout development. A symptom was considered unformed if the total score was less than 9. If the total score ranged from 10 to 15, the symptom was regarded as being in the process of formation, while a score of ⩾16 indicated that the symptom was fully developed. A total phase score of less than 36 was considered unformed, a score between 37 and 60 indicated the phase was in formation, and a total score above 60 suggested that the phase of emotional burnout was fully developed.

To assess the results of the anonymous survey on emotional burnout among paediatric ward nurses, two observation groups were formed. Group I consisted of 83 nurses working in non-infectious paediatric wards, while Group II included 52 nurses working in infectious paediatric wards. The average age of the nurses in Group I was 38.02 ± 0.9 years, with 98.8% being women. The average age of Group II was 43.81 ± 1.6 years ($p > 0.05$), with 92.2% women ($p\varphi > 0.05$), and their average length of service was 18.01 ± 0.9 years and 22.09 ± 1.4 years ($p > 0.05$), respectively. Thus, the groups were comparable based on the main characteristics.

The results of the study were analysed using biostatistical and clinical epidemiological methods with the software packages Statistica 10 by StatSoft and Excel XP for Windows, employing both parametric and non-parametric calculation methods. The Student's t-test was used to compare variables between groups for absolute values, while the Fisher criterion ($p\varphi$) was applied for relative values. Predictive values for various threshold levels of the obtained results were also calculated. Statistical significance was determined at $p < 0.05$.

Additionally, from a clinical epidemiology perspective, relative risk (RR) and odds ratio (OR) were assessed for the development of specific events, along with their respective 95% confidence intervals (CI).

The study was conducted following the principles of biomedical ethics and the fundamental provisions of the "Ethical Principles for Medical Research Involving Human Subjects", as established by the Helsinki Declaration (1964-2013), ICH GCP (1997), the European Economic Community Directive No. 609 (24 November 1986), and the orders of the Ministry of Health of Ukraine No. 690 (23 September 2009), No. 944 (14 December 2009), and No. 616 (3 August 2012) [11-13].

RESULTS

When assessing the three main phases of emotional burnout among paediatric ward nurses during the COVID-19 pandemic, it was found that nurses in non-infectious departments exhibited significantly higher scores across all phases of emotional burnout, specifically in the "tension", "resistance", and "exhaustion" phases (Fig. 1). Interestingly, the scores for Group I approached the threshold of final formation, being assessed within the range of 37-60 points. In contrast, the respondents in Group II showed that the phases of emotional burnout were virtually unformed.

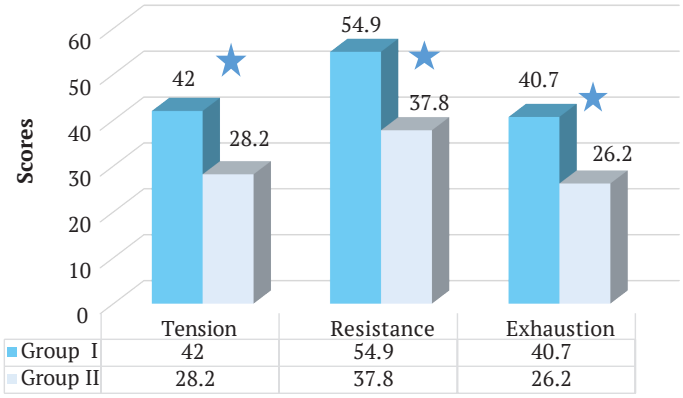


Figure 1. Comparative assessment of emotional burnout among paediatric ward nurses during the COVID-19 pandemic
Notes: ★ – significant difference ($p < 0.05$)
Source: compiled by the authors

The risk indicators for scoring ⩾37 points in the "tension" phase among nurses in Group I compared to those in Group II were as follows: RR – 1.9 (95% CI: 1.3-2.9), OR – 4.2 (95% CI: 2.2-7.7); for ⩾37 points in the "resistance" phase – RR – 1.9 (95% CI: 1.5-2.5), OR – 3.6 (95% CI: 1.9-6.4); for ⩾37 points in the "exhaustion" phase – RR – 1.5 (95% CI: 1.0-2.4), OR – 2.7 (95% CI: 1.4-4.9). Thus, the data indicated that among nurses in non-infectious wards during the COVID-19 pandemic, the risk of developing emotional burnout was higher than that of nurses working in infectious wards. These findings were likely linked to the greater level of awareness regarding coronavirus infection among healthcare workers in infectious departments and their training in responding to epidemiological threats. Further detailed assessment of the results from the anonymous survey regarding the "tension" phase revealed that the scores for three symptoms – levels of anxiety and depression, feelings of dissatisfaction with oneself, and the sensation of being "trapped" – in Group II nurses were recorded in the range of <9 points, indicating that these symptoms were not yet formed. Meanwhile, the score for "experiencing traumatic circumstances" fell within the stage of symptom formation (Fig. 2).

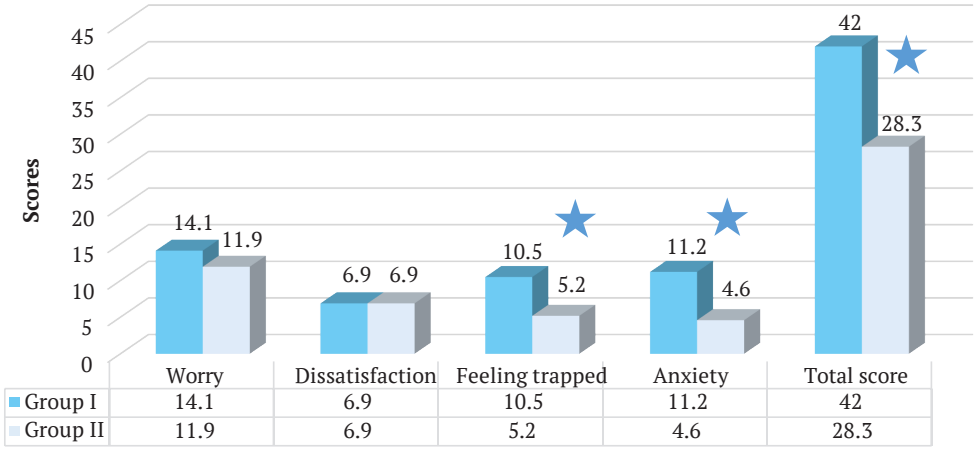
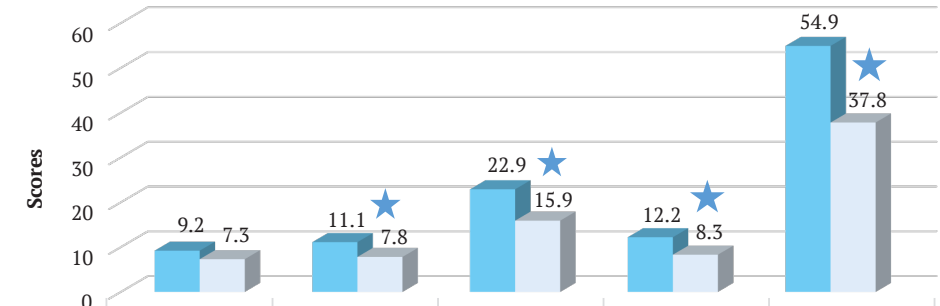


Figure 2. Score assessment of the "tension" phase of emotional burnout among paediatric ward nurses during the COVID-19 pandemic
Notes: ★ – significant difference ($p < 0.05$)
Source: compiled by the authors

At the same time, according to the results obtained, the overall score for the "tension" phase, as well as the individual symptom scores – such as the sensation of being "trapped", and levels of anxiety and depression – were significantly higher among nurses in Group I. The proportion of nurses in Group I who exhibited the initial signs of exhaustion in the "tension" phase, indicated by a total score >37 points, was 51.8%, while in Group II it was 25.0% ($p\varphi < 0.05$). Furthermore, the analysis revealed that a fully formed "tension" phase of emotional burnout (total score >60 points) was almost five times more frequently reported among respondents in Group I (28.9%) compared to 5.8% of respondents in Group II ($p\varphi < 0.05$).

A similar trend was observed in the assessment of symptoms in the "resistance" phase among the respondents (Fig. 3). Specifically, the scores for moral and emotional disorientation, the expansion of emotional conservation, and the reduction of professional responsibilities among nurses in infectious disease wards were significantly lower than those of the comparison group.

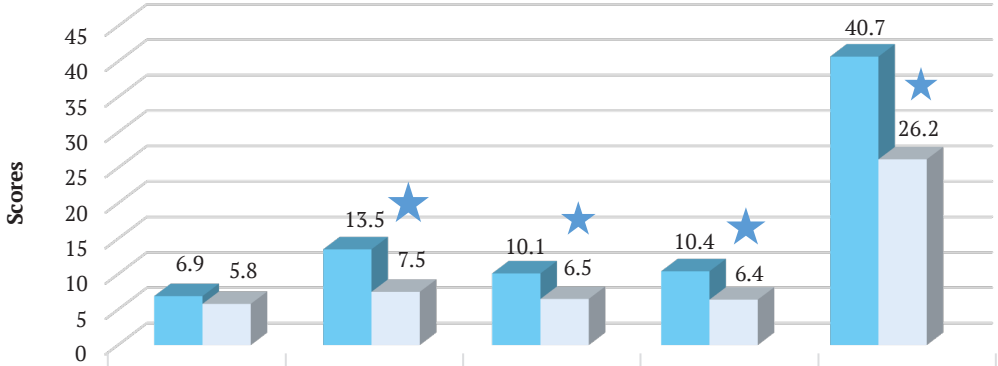


	Inadequate response	Disorientation	Emotional sphere	Reduction of responsibilities	Total score
Group I	9.2	11.1	22.9	12.2	54.9
Group II	7.3	7.8	15.9	8.3	37.8

Figure 3. Score assessment of the "resistance" phase of emotional burnout among paediatric ward nurses during the COVID-19 pandemic
Notes: ★ – significant difference ($p < 0.05$)
Source: compiled by the authors

Symptoms of the "resistance" phase, such as inadequate emotional response, emotional and moral disorientation, and reduction of professional responsibilities among nurses in infectious disease wards, were not fully formed, being 1.4 to 1.46 times less pronounced than those in the comparison group. The proportion of nurses in Group I who exhibited initial signs of exhaustion in the "resistance" phase, indicated by a total score >37 points, was 71.1%, while in Group II it was 46.2% ($p\varphi < 0.05$). Further analysis revealed that a fully formed "resistance" phase of emotional burnout (total score >60 points) was nearly twice as prevalent among respondents in Group I (38.6%) compared to 17.3% of respondents in Group II ($p\varphi < 0.05$).

This trend likely indicated a better theoretical and practical preparation of nurses for working in the conditions of the COVID-19 pandemic. The assessment of the "exhaustion" phase indicators among nurses in Group II – emotional detachment, personal depersonalisation, emotional deficit, and psychosomatic and psychological disturbances of the vegetative nervous system – did not reach 9 points, indicating that these symptoms were not expressed or fully formed (Fig. 4).



	Emotional deficit	Emotional detachment	Personal detachment	Psychosomatic disorders	Total score
Group I	6.9	13.5	10.1	10.4	40.7
Group II	5.8	7.5	6.5	6.4	26.2

Figure 4. Score assessment of the "exhaustion" phase of emotional burnout among paediatric ward nurses during the COVID-19 pandemic
Notes: ★ – significant difference ($p < 0.05$)
Source: compiled by the authors

At the same time, among the nurses in Group I, emotional detachment, personal depersonalisation, psychosomatic disorders, and psychological disturbances of the vegetative nervous system were recorded significantly more frequently, by a factor of 1.5 to 1.8.

The proportion of nurses who exhibited initial signs of the "exhaustion" phase (total score >37 points) among respondents in Group I was 42.2%, whereas in Group II it was 21.2% ($p\varphi < 0.05$). Further analysis revealed that a fully formed "exhaustion" phase of emotional burnout (total score >60 points) was almost twice as common among respondents in Group I (21.7%) compared to 11.6% of respondents in Group II ($p\varphi < 0.05$). Nurses in non-infectious paediatric wards during the COVID-19 pandemic exhibited

higher levels across all phases of emotional burnout compared to those in infectious wards, indicating greater resilience to stress among the latter.

DISCUSSION

Multicentre studies conducted before the COVID-19 pandemic have demonstrated that burnout is a global issue that significantly impacts the well-being of healthcare professionals. Specifically, based on 113 studies included in a systematic review and 61 studies examined in a meta-analysis, T. Woo *et al.* [14] showed that 11.23% of nurses worldwide experienced symptoms of burnout.

A systematic review conducted by U.O. Imo [15] revealed that the prevalence of burnout among nurses in the United Kingdom, particularly the phase of emotional exhaustion, ranged from 31% to 54.3% of respondents. The "resistance" phase, characterised by personal depersonalisation, was reported in 17.4-44.5% of cases, while feelings of self-dissatisfaction and emotional tension were found in 6-39.6% of nurses surveyed. These findings partially align with the results of the current study, especially those related to paediatric nurses in non-infectious wards. However, these symptoms were less pronounced among staff in infectious disease wards during the COVID-19 pandemic. The high prevalence of burnout among healthcare workers in normal times has become an even more significant challenge during epidemics, particularly in the context of the novel coronavirus infection caused by SARS-CoV-2.

At the same time, according to A. Aydin Sayilan *et al.* [16], more than half of the respondents exhibited signs of established emotional burnout syndrome. However, other researchers [14] reported that 78.5% of study participants exhibited only a mild level of emotional exhaustion. This partially aligns with the findings of this study, as nearly half of the patients in Group I displayed early signs of the onset of emotional burnout syndrome, in contrast to Group II, where such changes were noted in only one in four patients.

Findings regarding the characteristics of the "resistance" phase were further explored in studies by R. Chen *et al.* [17] and D. Hu *et al.* [18], who reported high levels of depersonalisation in 42% of respondents. Similar findings regarding the "resistance" phase were observed among the respondents in Group I of this study, where the figure was 38.6%. According to A. Bruyneel *et al.* [19], 38% of nurses had high levels of emotional exhaustion. The results obtained in this study showed that the fully developed "exhaustion" phase of emotional burnout was almost twice as prevalent among nurses in non-infectious wards.

The data regarding the impact of age and gender on the development of emotional burnout is quite contradictory. While A. Aydin Sayilan *et al.* [16] found that being under 30 years old and female were risk factors for emotional exhaustion, T. Sarboozi Hoseinabadi *et al.* [20] did not find a significant correlation between emotional burnout and age, sex, or education level. The authors of this study were unable to analyse this relationship due to the overwhelming majority of female respondents (over 90%).

Nurses undoubtedly faced challenges in maintaining emotional equilibrium as they were at a higher risk of contracting COVID-19 due to close patient contact during procedures and care. Consequently, they experienced significant anxiety about the potential consequences of the disease. The negative emotions of patients, colleagues, and family members further exacerbated stress and feelings of depression, increasing the likelihood of emotional burnout.

Psychological factors also contribute to nurse burnout. According to S. Kisely *et al.* [21], during the COVID-19 pandemic, nurses reported feelings of anxiety and depression, along with various psychosomatic disorders, which aligned with the results of this study and were most prominently expressed among the members of Group I.

Given that paediatric nurses represent a relatively small subset of the nursing profession, there is a dearth of research specifically focused on burnout among this group, particularly during the COVID-19 pandemic. However, paediatric nurses are a vulnerable population who have faced significant challenges due to the pandemic, experiencing a range of emotions such as fear, stress, and anxiety. As a result, they are at risk of professional burnout and may require psychological support or intervention [22].

As highlighted by the research of M. Bakhsh *et al.* [23], approximately half of paediatric nurses experienced psychosocial difficulties during the COVID-19 pandemic. The authors also emphasise the need for mental health support measures for healthcare workers during pandemics and other medical crises. However, according to studies by F.G.B. Góes *et al.* [24], nurses working with children and adolescents had a lower risk of experiencing emotional burnout compared to those working with other age groups.

Paediatric nurses, including those working in infectious disease wards, who participated in the study demonstrated a high level of professional competence when caring for patients with COVID-19 [25]. However, it was found that nurses with less experience had a higher risk of making professional errors when working with sick children and their families, and were more likely to consider leaving their jobs. This indicates that younger nurses require additional training and support from more experienced colleagues during a pandemic. Thus, numerous studies have reached a consensus that nurses working during a pandemic experience elevated levels of stress, anxiety, depression, and burnout, which can have long-term consequences.

The study aimed to investigate the presence and severity of emotional burnout among nurses working in paediatric infectious and somatic departments during the COVID-19 pandemic, to develop specific strategies to address this issue in the future. The findings indicated that among nurses in paediatric infectious disease wards, the primary phases of emotional burnout were not fully developed, and the risk of emotional burnout was lower compared to nurses in non-infectious children's wards. Conversely, nurses in non-infectious paediatric departments exhibited emotional detachment, depersonalisation, and psychosomatic and psychological disturbances of the vegetative nervous system with a likelihood 1.5 to 1.8 times greater. These results were likely associated with a higher level of awareness regarding the coronavirus among staff in infectious disease units and their experience in skills related to actions during epidemiological threats. Previous studies have shown that working in infectious paediatric wards increases the likelihood of learning aimed at improving or updating knowledge and skills related to infection control and COVID-19 (odds ratio – 3.8, relative risk – 2.0) [26].

Consequently, numerous COVID-19-related factors can contribute to the development of burnout among nurses. However, the pandemic's impact was less pronounced among nurses in infectious disease wards, where the risk of burnout was half that of nurses in non-infectious units. These nurses also demonstrated higher levels of personal achievement and knowledge of infection control and COVID-19. Higher levels of personal achievement are a powerful driver of professional growth, which may subsequently contribute to lower levels of burnout.

CONCLUSIONS

The findings revealed that nurses in non-infectious departments exhibited higher levels of emotional burnout at all stages compared to those in infectious disease departments, with significant differences in the severity and manifestation of burnout symptoms. It was determined that the stages of emotional burnout were more likely to be fully developed in nurses from non-infectious departments during the COVID-19 pandemic. According to the V. Boiko questionnaire, the score range was 40.7-54.9.

The assessment of symptoms in the "tension phase", including levels of anxiety and depression, feelings of dissatisfaction, and a sense of being "trapped", among nurses in infectious paediatric wards recorded scores of less than 9, indicating that these symptoms were not yet fully developed. The fully established phase of emotional burnout, characterised by a total score exceeding 60, was noted almost five times more frequently among respondents in Group I. The results of the assessment of the "resistance phase" of emotional burnout, particularly regarding moral-emotional disorientation, the expansion of emotional conservation, and the reduction of professional responsibilities among nurses in infectious wards, were significantly lower (by 1.4 to 1.46 times) compared to the respondents in the control group. At the same time, the fully developed phase of emotional burnout resistance (total score >60) was observed almost twice as frequently among respondents in Group I. The indicators of "exhaustion" related to emotional burnout, such as emotional detachment, personal depersonalisation, emotional deficiency, and psychosomatic and psychological disturbances of the vegetative nervous system, were 1.5 to 1.8 times higher in nurses from non-infectious departments.

The summary of the assessment of the formation of emotional burnout phases (⩾37 points for a phase) among nurses in Group I compared to those in Group II indicated an increased risk of this occurrence, with the following results: for the "tension" phase: relative risk – 1.9, with odds ratio – 4.2; for the "resistance" phase: relative risk – 1.9, with odds ratio – 3.6; and for the "exhaustion" phase: relative risk – 1.5, with odds ratio – 2.7. The prospects for further research involve identifying effective strategies for the psychological relief of nurses to reduce emotional burnout.

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None.

CONFLICT OF INTEREST

None.

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Оцінка ризиків розвитку емоційного вигорання в медичних сестер педіатричних відділень в період пандемії COVID-19

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Анотація. Проблема емоційного вигорання медичного персоналу є надзвичайно актуальною, особливо в період пандемії COVID-19, що визначило пріорітетність проведеного дослідження. Метою дослідження було проаналізувати результати анонімного анкетування медичних сестер педіатричних відділень щодо емоційного вигорання умовах пандемії COVID-19 з метою оптимізації їх роботи. Оцінка рівня емоційного вигорання проводилась шляхом аналізу результатів анонімного анкетування (анкета В. В. Бойко) 135 медичних сестер, які працюють в педіатричних відділеннях різного профілю лікувальних закладів м. Чернівці. Респонденти були розподілені на 2 групи спостереження. І групу сформували 83 медичні сестри, що працюють в дитячих відділеннях неінфекційного профілю, а 52 медичних сестри дитячих інфекційних відділень увійшли в ІІ групу. Середній вік медичних сестер І групи склав 38,02 ± 0,9 роки, а представників ІІ групи – 43,81 ± 1,6 роки ($p > 0,05$), а стаж роботи –18,01 ± 0,9 років та 22,09 ± 1,4 ($p > 0,05$) років відповідно. Встановлено, що серед опитаних респондентів І та ІІ груп показники оцінки всіх фаз емоційного вигорання були вірогідно вищими у медичних сестер неінфекційного профілю, зокрема фаз «напруження» (42 та 28,2 бали відповідно, ($p < 0,05$), «резистенції» (54,9 та 37,8 бали відповідно, ($p < 0,05$), та «виснаження» (40,7 та 26,2 бали відповідно, ($p < 0,05$). Показники ризику формування фаз емоційного вигорання (⩾37 балів) у медичних сестер І групи порівняно до представників ІІ групи дорівнювали: фаза «напруження»: відносний ризик – 1,9, співвідношення шансів – 4,2; фаза «резистенції»: відносний ризик – 1,9, співвідношення шансів – 3,6; фаза «виснаження»: відносний ризик – 1,5, співвідношення шансів –2,7. Встановлено, що у період пандемії COVID-19 серед медичних сестер неінфекційних відділень шанси реєстрації емоційного вигорання зростали у 2,7-4,2 рази

Ключові слова: коронавірусна інфекція; медичний персонал; професійне вигорання; стрес

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Morphology, pneumatization, septation, and protrusion of nearby structures into the sphenoid sinus: A retrospective radiological study

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Abstract. The morphology of the sphenoid sinus is critical in planning endoscopic sinus surgery, pituitary gland surgery, cerebrospinal fluid leak repair, the management of chronic sphenoid sinusitis, and the evaluation of skull base tumours. The objective of this study was to evaluate the morphology of the sphenoid sinus, with an emphasis on classification, septation, protrusion of structures, and dehiscence of the bony covering. In this retrospective radiological study, the morphology of the sphenoid sinus was analysed using 400 computed tomography scans. According to Hamberger's classification, the sphenoid sinus was classified into postsellar and presellar varieties. Additionally, the extent of pneumatization of the pterygoid process, anterior clinoid process, and greater wing of the sphenoid was noted. The anteroposterior, transverse, and vertical diameters of the sphenoid sinus were also measured. The relative positions of the genu of the internal carotid artery, vidian canal, and intracanalicular optic nerve were also recorded. The mean anteroposterior length, transverse length, and vertical length of the sphenoid sinus were found to be 29.3 (±2.8), 31.9 (±2.7), and 22.8 (±1.9) mm, respectively. The sellar type was found in 90% of subjects, while the remaining 10% had the presellar type. Only two subjects had the concha type of sinus. A single septum was noted in 32% of cases.

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Pneumatization of the pterygoid process was found in 22.5%, the anterior clinoid process in 27%, and the greater wing of the sphenoid in 21.25%. Optic nerve protrusion occurred in 24.5% of cases, and 23% of optic canals were dehiscent. The findings of this study hold significant relevance for neurosurgery, particularly in procedures involving the skull base, such as transsphenoidal surgery and optic nerve decompression

Keywords: paranasal air sinuses; anatomy; vidian canal; optic nerve; presellar; *sella turcica*

INTRODUCTION

The morphology of the sphenoid sinus has gained significance in recent years with the adoption of the endonasal endoscopic approach to the sphenoid sinus. The anatomy of the sphenoid sinus is crucial for surgeons operating at the base of the skull to address sinus inflammation, tumours, and pituitary gland surgery. Understanding the detailed morphology of the sphenoid sinus is essential to avoid complications and ensure safe navigation during these complex surgical procedures. Researchers K. Badran *et al*. [1] opined that pre-operative evaluation of the sphenoid sinus is essential for appropriate planning of approaches to skull base structures and for avoiding injury to nearby structures. The classification of the sphenoid sinus is typically based on its pneumatization pattern. According to Hamberger's classification, the sphenoid sinus is categorised into sellar, presellar, and postsellar types [2]. There are wide variations in the reported prevalence of these three varieties. S.B. Hiremath *et al.* [3] report 22.2% of presellar and 76.6% of sellar types among 500 patients. P. Thakur *et al*. [4] report 89.5% sellar variety. In addition, there are differences in the methodologies followed for the classification of the sphenoid sinus.

Pneumatization of the sphenoid sinus influences the position of structures related to the sinus, including the internal carotid artery, maxillary nerve, optic nerve, and vidian canal. O.C. Famurewa *et al.* [5] opine that a detailed evaluation of these structures is essential before the endonasal transsphenoidal approach to the skull base. According to N. Lakshman *et al.* [6], the extent of pneumatization in the sphenoid sinus and pterygoid process is closely associated with the type of vidian canal. P. Dahal *et al.* [7] have noted that pneumatization of the anterior clinoid process influences the type of optic nerve and reports a frequent association of type 3 optic nerve with a pneumatized anterior clinoid process. Y.J. Kang *et al*. [8] have reported that when sphenoid sinus pneumatization is inadequate, the intersphenoid septum is attached to the paraclival internal carotid artery or is found very close to the paraclival part. Additionally, S. Şimşek & A. İşlek [9] report age-related changes in sphenoid sinus pneumatization.

These findings suggest that the extent of sphenoid sinus pneumatization affects its relationship with nearby structures and that there are individual differences in this anatomy. Therefore, it is essential to assess the relationship between the optic nerve, vidian nerve, internal carotid artery, maxillary nerve, and sphenoid sinus in a specific population. Surgeons and radiologists must navigate this intricate landscape with precision, utilising advanced imaging techniques and classification systems to tailor interventions to individual anatomical variations. Consequently, this study was designed with the objectives of reporting the morphology of the sphenoid sinus, with an emphasis on classification, septation, protrusion of structures, and dehiscence of the bony covering.

MATERIALS AND METHODS

Study design: A total of 524 head computed tomography (CT) scans were analysed for sphenoid sinus morphology, and 400 scans were selected for measurements after excluding others according to the inclusion criteria. The study was conducted at AJ Institute of Medical Sciences and Research, Mangalore, from May 2022 to May 2024. Out of the 400 CT scans selected for the study, 256 cases were female and the rest were male. The mean age of the study group was 35.7 years, with ages ranging from 10 to 82 years. All patients were South Indians and Caucasians. Anatomical measurements and observations were performed on the coronal and axial sections of the CT scans.

Only scans with no radiologically detectable disease were included in the study. Patients with a history of sinus surgery, sinonasal tumours, nasal polyposis, severe cervical arthropathy, or head and neck injuries were excluded from the study. CT scans with 4-mm slices were reviewed, extending from the anterior frontal sinus to the anterior sphenoid sinus. Due to a lack of morphometric data in this area, the sections were spaced slightly further apart. For precise evaluation of adjacent structures and their relationship to the sphenoid sinus, contiguous transverse CT scans with a 2-mm slice thickness were analysed in an anteroposterior direction. Similarly, 2-mm coronal CT sections were examined for corresponding morphology and related structures. Each image was centred on the nasal cavity and supraorbital margin. Anatomical measurements and observations were conducted using both coronal and axial sections of the CT scans.

Pneumatization of the pterygoid process, anterior clinoid process, and greater wing of the sphenoid bone were observed in the selected CT scans. Sphenoid sinus classification based on Hamberger's classification was performed according to the type of pneumatization, which includes postsellar and presellar varieties. Bulging of the sella floor into the developed sinus is considered the sellar type. If the cancellous bone of the sphenoid extends from beneath the *sella turcica* to the anterior aspect of the floor, it is considered the presellar type. If the sphenoid sinus is absent and entirely filled with cancellous bone, it is classified as the concha type.

Septation of the sinuses was noted. In each CT scan, the dimensions of the sinuses, including the anteroposterior, transverse, and vertical diameters, were recorded. The anteroposterior diameter is measured from the anterior nasal spine to the posteriormost point on the wall of the sphenoid sinus in the axial plane. At the level of the pterygoid process in the coronal plane, the transverse diameter of the sphenoid sinus represents the distance between the lateral most points on the walls of the sphenoid sinus. The

vertical length is measured from the highest point of the sinus roof (the floor of the *sella turcica*) directly down to the lowest point on the sinus floor in the coronal section.

Additionally, details regarding the protrusion of the internal carotid artery, optic nerve, maxillary nerve, and vidian nerve were documented. Structures were considered to have protruded into the sphenoid sinus if a vertical line drawn through each structure in the coronal section showed a clear delineation between the structure and the sinus, with the line falling within the boundaries of the sinus. Dehiscence of the walls of the internal carotid artery, intracanalicular optic canal, vidian canal, and maxillary nerve was noted. If there was no visible bony structure separating the sinus from the evaluated structure, it was considered dehiscent. If the bone was too thin and the presence or absence of dehiscence could not be ascertained by two evaluators on two different occasions, such cases were accepted as instances of dehiscence. The distance from the anterior nasal spine to the rostrum of the sphenoid was measured. The presence or absence of Onodi cells (posterior ethmoid cells lying within the sphenoid sinus) was noted.

Analysis of data: All continuous data are expressed as means with standard deviations. In this retrospective radiological study, the morphology of the sphenoid sinus was analysed. Any right-left differences were evaluated using the t-test and chi-square test. The study protocol was approved by the institutional ethics committee (AJEC/Rev/30/2022). The study was conducted in line with the International Declaration of Helsinki [10], and all participants consented to participation.

RESULTS

A total of 400 CT scans were evaluated for sphenoid sinus morphology and its relationship with important neighbouring structures.

Sphenoid sinus dimensions: The mean anteroposterior length of the sphenoid sinus was 29.3 (±2.8) mm, with a maximum measured length of 39.56 mm and a minimum length of 22.12 mm. The mean transverse length of the sphenoid sinus was 31.9 (±2.7) mm, with a maximum measured length of 37.6 mm and a minimum length of 24.3 mm. The mean vertical length of the sphenoid sinus was found to be 22.8 (±1.9) mm, with a maximum measured length of 27.7 mm and a minimum length of 19.68 mm.

Sphenoid sinus classification: The sphenoid sinus is classified based on pneumatization. The sellar type was found in 90% of subjects. Pneumatization that is limited to the area anterior to the *sella turcica* is considered the presellar type. The presellar type was found in 10% of patients. Those with minimal or absent pneumatization are considered the conchal type. The conchal type was noted in 2 subjects (both females). There was no statistically significant difference between the types of sphenoid sinuses among males and females (sellar type $p = 0.58$ and presellar $p = 0.3$).

Septation of the sphenoid sinus: Among the scans analysed, there was only one septum in 32%, two septa in 23% (Fig. 1), three septa in 20%, and four septa in 7%. The total number of sinuses varies depending on the total number of septa (including accessory septa), which can differ in the anterior and posterior parts of the sphenoidal sinus. A single septum may bifurcate into two at the lower part of the sinus, as observed in 9 subjects.

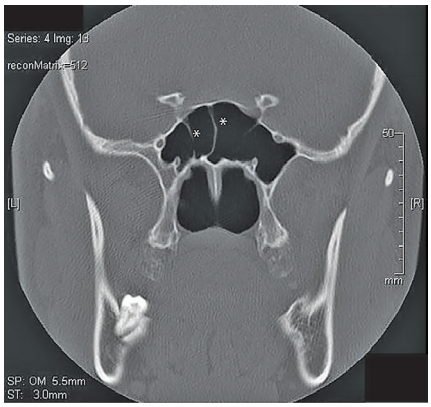

Figure 1. Coronal section of CT showing two septa in the sphenoid sinus
Notes: * indicates vertical sphenoid sinus septa
Source: image obtained from the Department of Radiology, evaluated by the authors of this study for paranasal sinus pathology, showing normal sphenoid sinus anatomy

Pneumatization details: 90 subjects (22.5%) had a pneumatized pterygoid process, of which 38 (9.5%) had bilateral pneumatization (Fig. 2), 32 (8%) patients showed left-sided pneumatization, and 20 (5%) patients exhibited right-sided pneumatization. The anterior clinoid process was pneumatized in 108 (27%) subjects. 42 (10.5%) subjects had bilateral pneumatization, 18 (4.5%) exhibited it only on the right side, and 25 (6.25%) on the left side. Pneumatization of the greater wing of the sphenoid bone was observed in 85 patients (21.25%). Among these, 38 patients (9.5%) exhibited bilateral pneumatization, 20 patients (5%) had pneumatization on the right side, and 32 patients (8%) had pneumatization on the left side. Statistically significant differences were found, with a higher prevalence of pneumatization on the left side for the anterior clinoid process, greater wing of the sphenoid, and pterygoid process compared to the right side.

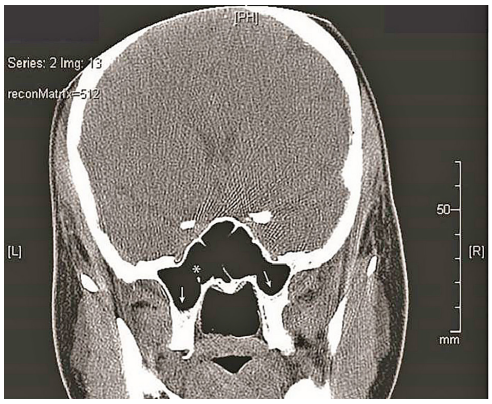

Figure 2. The coronal section of CT shows bilateral pneumatization of the pterygoid process and greater wing of the sphenoid with vidian canal protrusion
Notes: the white arrow indicates the pneumatized pterygoid process; * indicates the protruded vidian canal into the sphenoid sinus; R – right side; L – left side
Source: image obtained from the Department of Radiology, evaluated by the authors of this study for paranasal sinus pathology, showing normal sphenoid sinus anatomy

The protrusion and dehiscence observed are tabulated in Table 1. The optic nerve and vidian canal exhibited the greatest protrusion. The walls of the optic canal and vidian canal (Fig. 3) showed the highest dehiscence. The prevalence of optic nerve protrusion, optic nerve dehiscence, internal carotid artery dehiscence, maxillary nerve dehiscence, maxillary nerve protrusion, vidian canal protrusion, and vidian canal dehiscence were statistically different between the right and left sides.

Table 1. Protrusion and dehiscence observed during CT scan evaluation (n = 400)

	ON protrusion	ON dehiscence	ICA protrusion	ICA dehiscence	MN protrusion	MN dehiscence	VC protrusion	VC dehiscence
Bilateral	98 (24.5%)	92 (23%)	94 (23.5%)	37 (9.25%)	88 (22%)	39 (9.75%)	96 (24%)	42 (10.5%)
Left	36 (9%)	43 (10.75%)	42 (10.5%)	18 (4.5%)	26 (6.5%)	15 (3.75%)	30 (8%)	46 (11.5%)
Right	16 (4%)	56 (14%)	36(9%)	56 (14%)	34 (8.5%)	10 (2.5%)	52 (13%)	55 13.75%)
Total	150 (37.5%)	191(47.75%)	172 (43%)	111 (27.75%)	148 (37%)	64 (16%)	178 (44.5%)	143 (35.75%)

Notes: ON – optic nerve; ICA – internal carotid artery; MN – maxillary nerve; VC – vidian canal
Source: compiled by the authors

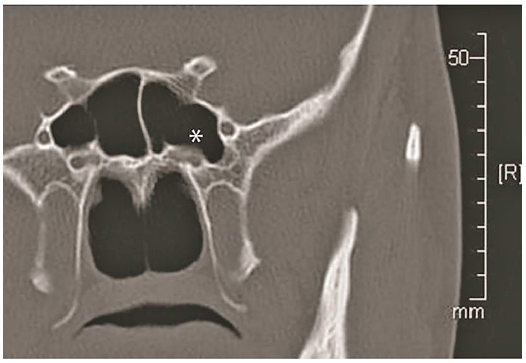

Figure 3. The coronal section of CT shows a dehiscent vidian canal on the right side
Notes: * indicates dehiscent vidian canal; R – right side
Source: mage obtained from the Department of Radiology, evaluated by the authors of this study for paranasal sinus pathology, showing normal sphenoid sinus anatomy

The mean distance from the anterior nasal spine to the rostrum of the sphenoid was 8.2 cm (range 7.6 to 1.5 cm). The mean inter-carotid artery distance was 14 mm (range 9 to 18 mm). A total of 53 cases showed Onodi cells, accounting for 13.25%. Onodi cells were bilateral in 24 cases. They were found on the right in 9 cases and on the left in 20 cases.

DISCUSSION

The classification of the sphenoid sinus into sellar, presellar, and conchal types is important in various clinical scenarios, particularly those involving endoscopic sinus surgery. The sellar type is the most advantageous for endoscopic sinus surgery because it provides optimal access to the sphenoid sinus and reduces the likelihood of complications. Due to its small size and limited access to the sphenoid sinus, the conchal type poses challenges for endoscopic sinus surgery [11]. In addition, the sellar type is the ideal variant for transsphenoidal surgery, as it provides direct access to the *sella turcica* without requiring extensive drilling. The presellar type requires more drilling to reach the *sella turcica*. According to O.C. Famurewa *et al.* [5] and G. Zada *et al.* [12], the conchal type is not suitable for transsphenoidal surgery due to the lack of access to the *sella turcica*. The reported prevalence of the sellar type varies widely. For instance, S.B. Hiremath *et al.* [3] report 76.6% as the complete sellar variety, while P. Thakur *et al.* [4] report 89.5% as the sellar variety. The authors of this study identified the sellar variety in 90% of subjects. The presellar type varies from 17% to 21%, and the conchal type varies from 2% to 28%. S. Sagar *et al.* [13] report the presellar variety in 26.3% of subjects, while S.B. Hiremath *et al.* [3] report the presellar variety in 22.2% of subjects. The authors of this study identified the presellar variety in 10% of subjects.

The pneumatization of the pterygoid process refers to the extension of pneumatic spaces into the pterygoid process of the sphenoid bone. The clinical significance of pterygoid process pneumatization is often related to its impact on adjacent structures and surgical considerations. Pneumatization can influence the anatomy of the skull base and may be relevant in procedures involving the sphenoid sinus or neighbouring structures. Additionally, variations in pneumatization are important for radiologists and surgeons to consider when interpreting imaging studies and planning interventions in the craniofacial region. In the present study, 27% of subjects were found to have pneumatized pterygoid processes. M.H. Alam-Eldeen *et al.* [14] report pneumatization in 61.6% of subjects. However, the study by A. Rahmati *et al.* [15] has shown a much lower rate of 38.9% pneumatization of the pterygoid process. Differences in populations considered, along with variations in the methodology of assessment, account for the wide range of prevalence reported in previous studies. Pneumatization increases with age, reaching its peak in adulthood. Though pneumatization is reported to commonly involve the medial pterygoid plate, this study did not attempt to report such differences in pterygoid plate pneumatization. Overall, the prevalence of pterygoid process pneumatization is generally considered common, and it is an aspect of normal anatomical variation. A well-pneumatized pterygoid process is considered an important anatomical corridor for accessing middle cranial fossa structures related to the cavernous sinus. For example, extended transnasal endoscopic techniques can access the pterygoid process via the medial aspect of the posterior maxillary wall. This study found a notable association between the presence of ipsilateral pneumatization of the pterygoid process and protrusion of the vidian canal.

Anterior clinoid process pneumatization occurs when air cells from the sphenoid and ethmoid sinuses extend into the anterior clinoid process. C.C. Shen *et al.* [16] reported that pneumatization can weaken the bone and increase the risk of cerebrospinal fluid (CSF) leaks during procedures such as optic nerve decompression and transsphenoidal surgery. Similarly, pneumatization can alter the anatomical relationships of important structures, such as the genu of the internal carotid artery and the intracanalicular part of the optic nerve, thereby increasing the risk of injury during surgery. Understanding the extent of anterior clinoid process pneumatization is crucial for planning and performing skull base surgeries safely. During optic nerve decompression, anterior clinoid process pneumatization can create a natural tunnel for the optic nerve, facilitating decompression surgery. However, A. Andrianakis *et al.* [17] report that such decompression also increases the risk of CSF leaks and requires careful drilling. In this study, 27% of the subjects examined had a pneumatized anterior clinoid process.

Protrusions and dehiscences in the walls of the sphenoid sinus are anatomical variations that can have significant clinical implications in various aspects of otolaryngology and neurosurgery. These altered relationships can increase the risk of injury to structures during surgery, particularly during endoscopic sinus surgery and transsphenoidal surgery. Protrusions can trap mucus and debris within the sinus, making it more susceptible to inflammation and infection, as noted by G. Hewaidi *et al*. [18]. Dehiscence can expose the underlying nerves to irritants from the sinus cavity, potentially contributing to trigeminal neuralgia. The prevalence of protrusions and dehiscences varies depending on the population studied and the imaging technique used. In the present study, it was observed that the maximum protrusion and dehiscence originated from the optic nerve among the structures related to the walls of the sphenoid sinus.

Septation of the sphenoid sinus can potentially hinder access to the *sella turcica*, making it more challenging to perform transsphenoidal surgery. This study observed various types of septation, and the details of individual septa aid in customising the transsphenoidal approach. A. Vaezi *et al*. [19] define the Onodi cell as an anatomical variant where the posterior ethmoid sinus pneumatizes into the sphenoid bone. Additionally, the presence of multiple septa or chambers within the sinus can complicate its morphology, necessitating detailed preoperative assessments for safe surgical interventions. In an Indian study, R.M. Itagi *et al.* [20] reported that 33.3% of subjects had Onodi cells. However, this study found a much lower prevalence of Onodi cells.

The classification and pneumatization patterns of the sphenoid sinus, pterygoid process, and anterior clinoid process are crucial for both clinical and surgical planning, particularly in endoscopic sinus surgery and transsphenoidal procedures. Understanding the variations in sphenoid sinus types – sellar, presellar, and conchal – is essential for optimising surgical access and minimising risks, with the sellar type being the most favourable for both sinus and skull base surgeries. While common anatomical variations, the pneumatization of the pterygoid process and the anterior clinoid process can significantly alter the relationship of critical neurovascular structures, increasing the risk of complications such as CSF leaks and nerve injuries. Careful preoperative assessment, including detailed imaging studies, is imperative for safe and effective surgical interventions. Additionally, septations, dehiscences, and protrusions in the walls of the sphenoid sinus, as well as the presence of Onodi cells, further complicate surgical approaches and highlight the importance of individualised planning to prevent complications and ensure successful outcomes. Understanding these variations provides a foundation for safer and more precise skull base surgeries.

CONCLUSIONS

In line with the objectives of the study, the morphology of the sphenoid sinus has been reported with an emphasis on classification, septation, protrusion of structures, and dehiscence of the bony covering. The mean anteroposterior length, transverse length, and vertical length of the sphenoid sinus were found to be 29.3 (±2.8), 31.9 (±2.7), and 22.8 (±1.9) mm, respectively. The sellar type was observed in 90% of subjects, while the presellar type was found in 10% of patients, and the conchal type was noted in 2% of subjects. Pneumatization of the pterygoid process was identified in 22.5%, the anterior clinoid process was noted in 27%, and the greater wing of the sphenoid was noted in 21.25%. Protrusion of the optic nerve was found in 24.5%, and 23% of optic canals were dehiscent. Protrusions and dehiscences in key structures, such as the optic nerve and vidian canal, were observed in a substantial number of subjects, with 47.75% showing optic nerve dehiscence and 44.5% exhibiting vidian canal protrusion. The study also revealed that the septation of the sphenoid sinus varied, with 32% of cases showing one septum, 23% with two septa, and fewer subjects presenting with three or four septa, which could complicate surgical access.

The findings of this study hold significant relevance for neurosurgery, particularly in procedures involving the skull base, such as transsphenoidal surgery and optic nerve decompression. The presence of anatomical variations, such as pneumatization of the pterygoid and anterior clinoid processes, along with septations and dehiscences, presents potential challenges. These variations can alter the proximity and vulnerability of critical neurovascular structures, including the optic nerve, internal carotid artery, and vidian canal, increasing the likelihood of complications, such as cerebrospinal fluid leaks, nerve injuries, and vascular damage during surgery. Future research could explore the impact of these anatomical variations on long-term surgical outcomes, particularly in high-risk patients. Additionally, studies involving larger, more diverse populations may provide deeper insights into the prevalence and clinical significance of these variations across different demographics.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Морфологія, пневматизація, септація, виступ сусідніх структур у клиноподібну пазуху – ретроспективне радіологічне дослідження

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Анотація. Морфологія сфеноїдного синуса є критично важливою для планування ендоскопічної синусної хірургії, хірургії гіпофіза, ремонту витоків ліквору, лікування хронічного сфеноїдного синуситу та під час оцінки пухлин основи черепа. Метою цього дослідження було оцінити морфологію сфеноїдного синуса з акцентом на класифікацію, перегородки, випинання структур та деісценцію кісткового покриття. У ретроспективному радіологічному дослідженні було проаналізовано морфологію сфеноїдного синуса, використовуючи 400 комп'ютеризованих томографій. Згідно з класифікацією Гамбергера, сфеноїдний синус було класифіковано на постселерний і преселерний варіанти. Крім того, було зафіксовано ступінь пневматизації крилоподібного відростка, переднього клиноподібного відростка та більшого крила сфеноїдної кістки. Відзначалися антеропостеріорні, поперечні та вертикальні діаметри сфеноїдного синуса. Відносне положення гену внутрішньої сонної артерії, видіан каналу та інтраканалярного зорового нерва також було зафіксовано. Середня антеропостеріорна довжина, поперечна довжина та вертикальна довжина сфеноїдного синуса склали 29,3 (±2,8), 31,9 (±2,7) та 22,8 (±1,9) мм відповідно. Тип селеру був виявлений у 90 % суб'єктів, а решта 10 % мали тип преселери. Лише у двох суб'єктів був виявлений тип конхи. Одна перегородка була зафіксована у 32 %. Пневматизація крилоподібного відростка спостерігалася у 22,5 %, переднього клиноподібного відростка – у 27 %, а більшого крила сфеноїдної кістки – у 21,25 %. Випинання зорового нерва спостерігалося у 24,5 %, а 23 % зорових каналів мали деісценцію. Результати цього дослідження мають значну важливість для нейрохірургії, зокрема, для процедур, що стосуються основи черепа, таких як транссфеноїдальна хірургія та декомпресія зорового нерва

Ключові слова: параназальні повітряні синуси; анатомія; видіан канал; зоровий нерв; преселер; *sella turcica*

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Investigation of antigen-presenting cells in the intestinal mesentery in normal and adhesive processes

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Abstract. The morphology and topography of dendritic cells in the mesentery of the small intestine, their quantity, and their presence under normal conditions and during progressive adhesive processes have been insufficiently studied, presenting an important issue in immunomorphology. This study aimed to identify and determine the functional activity of antigen-presenting cells using lectin histochemistry with peanut and lentil lectins under normal conditions and during adhesive processes. The methods employed included morphometric analysis, lectin histochemistry, and statistical analysis. For the first time, using lectin histochemistry with lentil and soy lectins, functionally active and immunologically immature antigen-presenting cells were found in the structure of lymphoid clusters of the small intestine mesentery. A correlation was established between the progression of adhesion processes and the number of antigen-presenting cells. Correlation between dendritic cells and the quantity of immunologically immature lymphocytes and B-lymphocytes was identified, enhancing the understanding of the functional mechanisms of the local arm of innate immunity. An increasing trend in immunologically immature lymphocytes and B-lymphocytes was observed alongside an increase in antigen-presenting cells. The results indicated that the activation of dendritic cells in mesenteric tissues induced an increase in immunologically immature lymphocytes, from which B-lymphocytes subsequently developed, initiating a local immune response. The increased frequency of PNA+- and LCA+- antigen-presenting cells pointed to an elevated immune reactivity of lymphoid clusters. This study on the distribution of antigen-presenting cells contributes to a deeper understanding of the structure of lymphoid tissue associated with serous membranes, as well as fat-associated lymphoid aggregates, and underscores the connection between innate and adaptive immunity in the abdominal cavity

Keywords: peritoneum; dendritic cells; immunity; lectins; rats; lymphocyte; histological changes

INTRODUCTION

A.S. Kashyap *et al.* [1] demonstrated in their study that the serous membrane of the abdominal cavity has a large total surface area, and therefore, reactive changes in its lymphoid component have both local and systemic implications. A detailed study of the structure and reactive changes of the lymphoid tissue will help to understand the local mechanisms of innate and acquired mucosal immunity. Research by D. Repáraz *et al.* [2] indicates that the peritoneal cavity contains various lineages of dendritic cells with different origins, however, their morphological and functional characteristics remain incompletely understood.

T.J. Yun *et al.* [3] have confirmed in their research that dendritic cells originate from haematopoietic stem cells, except follicular dendritic cells which have a mesenchymal origin. Antigen-presenting cells develop from progenitor cells of both the myeloid and lymphoid lineages. Dendritic

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cells are one of the most important factors in the processes of proliferation, differentiation, and selection of lymphocytes.

M.K. Jawanda *et al.* [4] investigated that lentil lectin is a marker that can be used to detect the carbohydrate residue α-D-mannose, and is used to identify dendritic cells as it is found in the structure of the cytoplasmic membrane and cytoplasm receptors. To date, dendritic cells in individual structures of the peritoneum remain incompletely studied. In the mesentery of the small intestine, the detection and role of dendritic cells have not yet been investigated, which is a current issue in immunomorphology. M. Simplicien *et al*. [5] in their study confirm that dendritic cells express receptors that help adsorb exogenous antigens – C-type mannose lectin receptors (concanavalin and lentil lectin receptors). During functional maturation, dendritic cells form numerous processes (5 to 7) that acquire an elongated, thickened form, and present antigenic material, thereby inducing both T-cell and B-cell arms of the immune system.

M. Liu *et al.* [6] described serosa-associated lymphoid clusters (SALC) and fat-associated lymphoid clusters (FALC) as important centres providing the first line of defence in the structure of mucosal membranes through both innate and adaptive immunity. L.H. Jackson-Jones *et al.* [7] characterised fat-associated lymphocyte aggregates, or milky spot-like structures, present in the adipose reservoirs of the peritoneum, pericardium, mediastinum, and pleura. These structures are characterised by structural similarity, contain various subpopulations of lymphocytes, and perform functions akin to those of SALC. D. van Uden *et al.* [8] found that the composition of these aggregates plays a crucial role in the microenvironment of lymphoid clusters. This issue requires further detailed investigation. Dendritic cells within the lymphoid clusters serve as a tissue barrier between the intestine and the abdominal cavity, operating at the interface of innate and adaptive immunity [9].

The morphology, topography, and quantity of dendritic cells in the small intestine mesentery, both in normal conditions and during progressive adhesion formation, remain insufficiently studied. This study aimed to identify antigen-presenting cells, determine their functional activity using lectin histochemistry with peanut and lentil lectins, and investigate the ratio of antigen-presenting cells to the total number of lymphocytes, immunologically immature PNA^+-lymphocytes, and SBA^+-B-lymphocytes in both normal and adhesion conditions.

MATERIALS AND METHODS

The study was conducted over a period of six months in 2023 (from May to October) and involved sexually mature male white rats at the laboratory of the Department of Physiology, Immunology, and Biochemistry with a course in Civil Defence and Medicine at Zaporizhzhia National University. The study model is presented in Table 1.

Table 1. Study model of experimental adhesion formation

Group	Number of animals (n)	Housing conditions	Injection
Intact (I)	5	Relative humidity of (55 ± 5)% at t = 22°C, 12-hour light cycle, unrestricted access to water; standard diet of complete granulated compound feed	No injection
Experimental (II)	15		A single injection of 0.5 mL of 20% talc suspension into the abdominal cavity
Control (III)	5		Physiological saline

Source: compiled by the authors

Animals were euthanised on the 7th, 14th, and 21st days after injection, using chloroform. Autopsy and sample collection were performed following the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, general ethical principles of animal experimentation adopted by the First National Congress of Ukraine on Bioethics [10].

For histological analysis, 15×15 mm tissue fragments of the small intestine mesentery were used to create thin-film preparations. To prevent distortion of the thin film fragments, the materials were placed on a foam base, after which they were fixed in 10% formalin solution.

Visualisation of lymphoid clusters SALC and FALC was performed by washing off the mesothelial layer after treating the mesenteric tissue of the small intestine with a trypsin enzyme solution. Histochemical identification of lectin receptors on thin-film preparations was conducted according to the method of O. Lutsyk [11]. Prepared lectin solutions were applied to the treated mesenteric samples and incubated for 45 minutes at 37°C. The reaction results were visualised using diaminobenzidine. To study the distribution of dendritic cells in the small intestine mesentery that carry receptors for β-D-galactose, peanut agglutinin (PNA) was used, while *Lens culinaris* agglutinin (LCA) was applied to identify dendritic cells with the ability to present antigens via α-D-mannose receptors, using the standard RPC "Lectinotest" kit (Lviv, Ukraine). A positive histochemical reaction was identified by the presence of a benzidine marker on the surface of cytoplasmic membranes and in the cytoplasm. The functional activity of dendritic cells was determined by analysing their morphological characteristics, such as size, staining intensity, and the number and length of projections. The preparations were studied using light microscopy, accompanied by microphotography of samples from each group using the MICROmed Evolution LUM LS-8530 microscope (Ukraine). The number of antigen-presenting cells was counted using a morphometric grid over a standard area of 10,000 μm^2. For statistical processing, previously obtained and published data on the total number of lymphocytes, PNA^+ immunologically immature lymphocytes, and SBA^+ B-lymphocytes were utilised [12, 13]. Statistical analysis was conducted using Student's t-test with Microsoft Excel, and results were considered significant at $p \leq 0.05$.

RESULTS

Morphologically, PNA^+- antigen-presenting cells are characterised by a star-shaped form both under normal conditions and during the modelling of the adhesion process. In the intact group of animals, these cells

appear more rounded, with almost no visible projections (Fig. 1a). In both the PNA⁺-antigen-presenting cells of the intact group (Group I) and the experimental group (Group II), brown benzidine granules were observed on the surface of the cell's cytoplasmic membrane. The number of PNA⁺-antigen-presenting cells in the intact group was 2.74 ± 0.04 per 10,000 μm², which served as a reference point for comparison with animals at various stages of experimental adhesion formation. On the 7th day, the cells in the experimental group (Group II) displayed a star-shaped morphology. Their petal-shaped nuclei and projections were clearly visualised against the background. The cytoplasm contained light-brown benzidine granules, while the plasma membrane was dark brown. The number of cells increased compared to the intact group, reaching 3.1 ± 0.08 per unit area. By the 14th day, the PNA⁺-antigen-presenting cells in Group II became more elongated with numerous projections. Benzidine granules imparted a brown hue to the cytoplasmic membrane and cytoplasm. The petal-shaped nuclei and dotted projections were well visualised (Fig. 1b). The somas of the PNA⁺-antigen-presenting cells were spaced up to 11 μm apart, with their projections appearing to connect, forming a network of intercellular contacts. The number of cells during this stage of adhesion formation slightly increased compared to the 7th day and the intact group, reaching 3.3 ± 0.07 per unit area.

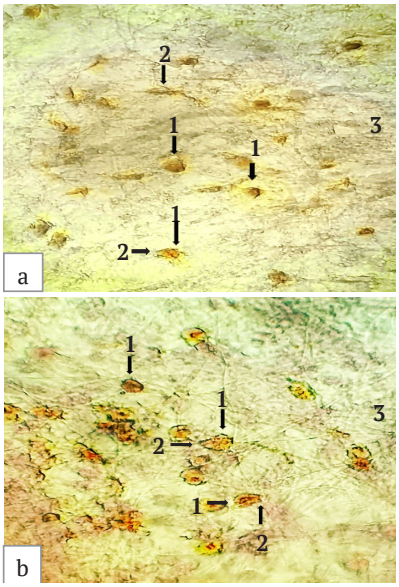

Figure 1. Film preparation of rat mesentery
Notes: a) PNA+-antigen-presenting cells under normal conditions; b) PNA+-antigen-presenting cells on day 14 of the adhesion modelling process: 1. soma and fragments of antigen-presenting cells; 2. sites of process emergence and processes; 3. submesothelial layer. Lectin histochemistry with Mayers haematoxylin nuclear counterstaining following mesothelium desquamation by trypsin. Magnification x100
Source: authors' material

On the 21st day of the study, similar cell morphologies were observed in the experimental group as seen on the 14th day of adhesion process modelling. The PNA⁺-antigen-presenting cells displayed an elongated, slightly flattened shape with numerous winding projections. The increased length of cytoplasmic projections indicates activation of PNA⁺-antigen-presenting cells, reflecting the reactive changes in the lymphoid component of the small intestinal mesentery. The benzidine granules accumulated maximally on the cells' cytoplasmic membrane and were also present in the cytoplasm, giving the cells a dark-brown hue against the generally light background of the submesothelial layer of the small intestinal mesentery. It was determined that the number of PNA⁺ antigen-presenting cells at this stage of the study reached 3.5 ± 0.02 per unit area.

As a result of the lectin histochemical study, it was found that in the intact group, under normal conditions, LCA⁺-antigen-presenting cells measuring 10-15 μm with an irregular elongated shape and several (3-4) angles were identified (Fig. 2a). Petal-shaped nuclei and sites of projection emergence were clearly visible. Benzidine granules accumulated on the surface of the plasma membrane and within the cytoplasm, appearing as brown-coloured granules. In the mesentery of the small intestine in the intact group (Group I), there were 2.05 ± 0.02 LCA⁺-antigen-presenting cells per unit area. On the 7th day of adhesion process modelling in the experimental group (Group II), the LCA⁺ antigen-presenting cells became more distinct and prominent, as the cells acquired a dark brown hue. They were characterised by a more rounded or elongated shape, with wavy projections being visible. Cells bearing receptors for lentil lectin (LCA⁺) were observed to cluster around the vascular lumen (Fig. 2b). The number of these cells at this stage of the adhesion process increased compared to the intact group, reaching 2.68 ± 0.02 cells per unit area.

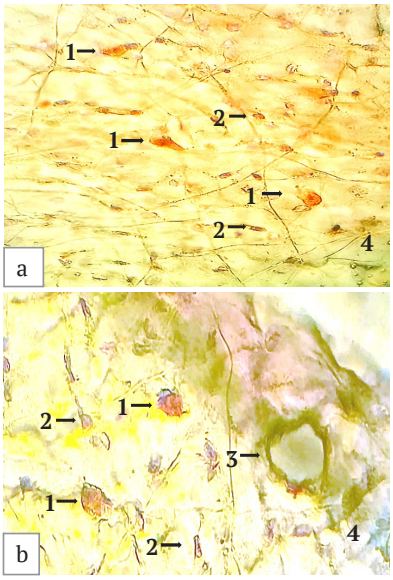

Figure 2. Small intestine mesentery. Film preparation
Notes: a) under normal conditions; b) on the 7th day of adhesion process modelling. Lectin histochemistry with Mayers haematoxylin nuclear counterstaining following mesothelium desquamation by trypsin: 1. somas of LCA⁺-antigen-presenting cells; 2. fragments of LCA⁺-antigen-presenting cells; 3. vascular lumen; 4. submesothelial layer. Magnification x100
Source: authors' material

During the study, on the 14th day in Group II (experimental group), LCA+-antigen-presenting cells of typical morphology were identified, comparable to the previous stage of the adhesion process. Mannose receptors were detected on the surface of the cytoplasmic membrane and within the cytoplasm. Isolated LCA+-antigen-presenting cell somas were observed, with nearby wavy, dotted projections. The intensity of benzidine granule accumulation on the cell membrane and in the cytoplasm, as well as the density of LCA+-antigen-presenting cells, increased (+++) compared to the intact group (+) and the 7th day of the study (++). The number of LCA+-antigen-presenting cells at this stage of adhesion process modelling reached 4.35 ± 0.01 cells per unit area.

On the 21st day of the study, in the animals from Group II (experimental group), clusters of LCA+-antigen-presenting cells (3-4 cells) were detected around the branching blood capillaries of the small intestine mesentery. Cells were identified with crescent-shaped or polygonal morphology, featuring 4-6 projections extending from the cell body. A visible increase in the number and thickness of dendritic cell projections was noted. At this stage of the adhesion process, a progressive rise in the number of polygonal LCA+-antigen-presenting cells was observed, with their quantity reaching 5.8 ± 0.03 cells per unit area. Based on the statistical data obtained, a correlation was established between the numbers of PNA+-antigen-presenting cells and LCA+-antigen-presenting cells, counted per standard area of 10,000 μm² (Fig. 3).

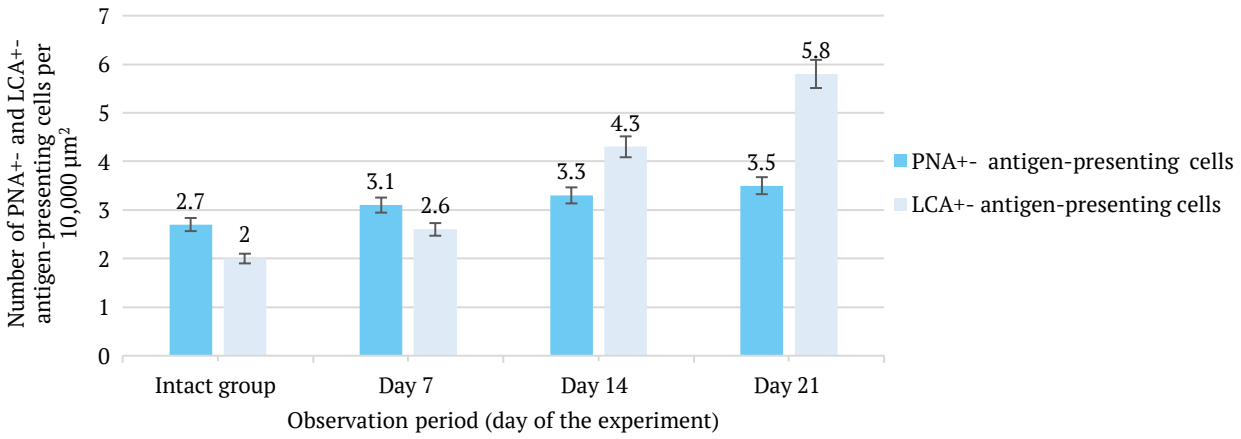

Figure 3. The ratio of PNA+- and LCA+-antigen-presenting cells in the small intestine mesentery under normal conditions and at different time points of adhesion process observation
Source: compiled by the authors

Thus, the number of PNA+-antigen-presenting cells in the small intestine mesentery of animals in both the intact group and those undergoing the experimental adhesion process did not show statistically significant changes. Under normal conditions in the intact group (Group I), the ratio of PNA+- to LCA+-antigen-presenting cells was observed to be 1:1. However, in the experimental group (Group II), the number of LCA+-antigen-presenting cells increased, with ratios of PNA+- to LCA+-antigen-presenting cells observed at 1:2 on day 14 and 1:3 on day 21 of the study, respectively. Upon analysing the number of LCA+-antigen-presenting cells, it can be concluded that these cells become functionally more active during the experiment. Their activity in presenting antigens to lymphocytes increases, which enhances their visualisation and leads to an increase in their numbers compared to the baseline.

Based on previously obtained and published data regarding the total number of lymphocytes, the quantity of PNA+-immunologically immature lymphocytes, and SBA+-B-lymphocytes [13, 14], as well as the newly acquired data on the number of PNA+- and LCA+-antigen-presenting cells per unit area, a coefficient ratio between these immune components within the lymphoid clusters of the small intestine mesentery was analysed (Table 2). Comparing the ratios of antigen-presenting cells to PNA+-immunologically immature lymphocytes and SBA+-B-lymphocytes reveals a certain pattern. On average, in both the intact and experimental groups, there are two PNA+-immunologically immature lymphocytes and two SBA+-B-lymphocytes for every identified antigen-presenting cell. By day 7 of the experiment, an increase in the number of SBA+-B-lymphocytes per LCA+-antigen-presenting cell is observed in the experimental group.

Table 2. The ratio of PNA+-antigen-presenting cells and LCA+-antigen-presenting cells to the total number of lymphocytes, PNA+-immunologically immature lymphocytes, and SBA+-B-lymphocytes

		PNA+- antigen-presenting cells	LCA+- antigen-presenting cells
Group I (intact)	Total number of lymphocytes	1:3	1:4
	PNA+-lymphocytes	1:2	1:2
	SBA+-lymphocytes	1:2	1:2

Table 2. Continued

			PNA⁺- antigen-presenting cells	LCA⁺- antigen-presenting cells
Group II (experimental)	Day 7	Total number of lymphocytes	1:3	1:3
		PNA+-lymphocytes	1:2	1:2
		SBA+-lymphocytes	1:2	1:3
	Day 14	Total number of lymphocytes	1:3	1:4
		PNA+-lymphocytes	1:2	1:2
		SBA+-lymphocytes	1:3	1:2
	Day 21	Total number of lymphocytes	1:2	1:4
		PNA+-lymphocytes	1:2	1:1
		SBA+-lymphocytes	1:2	1:2

Source: compiled by the authors

It is also noted that by day 14 in group II, the number of SBA⁺-lymphocytes increased, with three SBA⁺-B-lymphocytes corresponding to one PNA⁺-antigen-presenting cell. By day 21 of the study, the number of PNA⁺-immunologically immature lymphocytes and SBA⁺-B-lymphocytes remains consistent with the previous stages of adhesion formation. The increase in the number of identified PNA⁺- and LCA⁺-antigen-presenting cells during adhesion processes indicates heightened immunoreactivity of immune tissue associated with SALC and FALC.

DISCUSSION

For the first time, using lectin histochemistry, LCA⁺-antigen-presenting cells and PNA⁺-antigen-presenting cells were detected in the lymphoid tissue associated with serous membranes (FALC and SALC) of the small intestine mesentery. A correlation was established between the progression of adhesion formation and the number of LCA⁺- and PNA⁺-antigen-presenting cells.

The Poltava school of morphologists, led by Professor I. Ksyonz *et al.* [14], conducted studies of lymphoid clusters in the structures of the greater omentum, as one of the components of the peritoneum. Similar studies by Brazilian scientists A.W. Wang *et al.* [15] confirm that the omentum contains a large number of immunocompetent cells in its lymphoid clusters: macrophages, antigen-presenting cells, and lymphocytes of various subpopulations. J.L. Suen *et al*. [16] in their study substantiate that with a change in the reactivity of the lymphoid component of the tissues of the small intestine mesentery, activation of antigen-presenting cells is observed. Their visualisation and number per unit area increase, which is associated with the activation of receptors on the cell surface in response to an antigen.

Analysis of the number of PNA⁺-antigen-presenting cells and LCA⁺-antigen-presenting cells confirms that they become functionally more active under antigenic load. Their activity in presenting antigens to lymphocytes increases, resulting in improved visualisation and a rise in their numbers compared to normal levels. It has been established that PNA⁺-antigen-presenting cells exhibit a stellate shape in both normal conditions and during the modelling of adhesion processes. In the intact group of animals, these cells appear more rounded, with their processes barely visible. As the adhesion process progresses, PNA⁺-antigen-presenting cells adopt an elongated, slightly flattened form. The number of convoluted processes is visually observed to increase and thicken. By the 21st day of the study, the quantity of PNA⁺-antigen-presenting cells reaches 3.5 ± 0.02 per investigated unit area, while in the intact group, the figure stands at 2.74 ± 0.04 per unit area. In the intact group, LCA⁺-antigen-presenting cells are noted to be irregularly elongated and polygonal in shape, characterised by petal-like nuclei, with the sites of their processes clearly visible. During the adhesion process, the antigen-presenting cells assume a crescent shape and become polygonal. There is also an increase in both the quantity and thickness of their cytoplasmic processes. Localisation of 3-4 LCA⁺-antigen-presenting cells is observed around the branching points of blood capillaries within the mesentery of the small intestine. At this stage of adhesion formation, there is a noted increase in the number of identified LCA⁺-antigen-presenting cells, reaching 5.8 ± 0.03 per investigated unit area, compared to the intact group of animals, which shows 2.05 ± 0.02 cells per unit area. L. Lamendour *et al.* [17] explained in their research that an increase in the number of antigen-presenting cells in response to antigenic load indicates an upregulation of immunity and the recognition of changes in the antigenic profile of surrounding cells.

When analysing the coefficient ratio between immunocompetent cells that are part of the lymphoid clusters of the small intestine mesentery SALC and FALC, it was established that in both the intact and experimental groups of animals, for one defined antigen-presenting cell, there are two PNA⁺-immunologically immature lymphocytes and two SBA⁺-B-lymphocytes. There is a growth in the quantitative indicators of SBA⁺-B-lymphocytes per one LCA⁺-antigen-presenting cell (3:1) and one PNA⁺-antigen-presenting cell (3:1).

D. Sancho & C. Reis e Sousa [18] noted in their research that dendritic cells play a key role in binding and presenting antigens, and also express numerous receptors in the cytoplasm. These receptors belong to the Toll- and cytokine receptor families (TLR3, TLR7, TLR8, TLR10, Myd88, IL7R-α, IL10, etc.) and C-lectins. C-lectin family receptors exhibit specificity for carbohydrate residues of β-glucan, α-D-mannose, and N-acetyl-glucosamine, which allows the use of lectin histochemistry for the detection of dendritic cells. M. Binnewies *et al.* [19] emphasise that dendritic cells are one of the most important factors in the process of proliferation, differentiation, and selection of lymphocytes. As previously found by P.A. Laginha *et al.* [20], activation of antigen-presenting cells is accompanied by an increase in

the number of cytoplasmic processes and their thickness, allowing them to connect with lymphocytes, forming intercellular contacts, thereby activating immunologically immature lymphocytes and B-lymphocytes.

The results of the study confirm this statement. On the 21st day of the study in the experimental group, PNA+-antigen-presenting cells with numerous winding processes were detected. LCA+-antigen-presenting cells were found with 4-6 processes extending from the soma. Visually, an increase in the number and thickness of the processes of both types of dendritic cells was noted. The increase in the length of cytoplasmic processes indicates the activation of antigen-presenting cells, which is expressed by reactive changes in the lymphoid component of the small intestine mesentery.

Z. Qiaomei *et al.* [21] note that the activation of dendritic cells in tissues leads to an increase in the number of immunologically immature lymphocytes, from which B-lymphocytes subsequently develop, triggering a local immune response. According to the obtained data, there is a growth in the quantitative indicators of PNA+-lymphocytes and SBA+-lymphocytes against the background of an increase in antigen-presenting cells. Thus, on the 7th day of the study, there is an increase in the number of SBA+-B-lymphocytes per one LCA+-antigen-presenting cell. On the 14th day, there are already three SBA+-B-lymphocytes per one PNA+-antigen-presenting cell. On the 21st day of the study, the number of PNA+-immunologically immature lymphocytes and SBA+-B-lymphocytes remains the same as in the previous terms of modelling the adhesion process. Thus, the opinion of A. Gardner *et al.* [22] confirmed that the increase in the number of immunologically immature lymphocytes, which subsequently become B-lymphocytes and initiate a local immune response, leads to the activation of dendritic cells in tissues. Analysis of the studied indicators made it possible to identify a relationship between the number of dendritic cells and PNA+- and SBA+-lymphocytes, which also complemented the understanding of the mechanism of functioning of the local link of innate immunity.

The study of the distribution of antigen-presenting cells has expanded our understanding of the structure of lymphoid tissue associated with SALC and FALC, highlighting the connection between the innate and adaptive immune systems within the abdominal cavity. The increased frequency of detection of PNA+- and LCA+-antigen-presenting cells during adhesion formation indicates an increase in the immunoreactivity of immune tissue associated with the serous membranes SALC and adipose tissue FALC. Based on the structural characteristics of the lymphoid clusters of SALC and FALC, mesothelial surroundings, and the presence of SBA+-B lymphocytes, PNA+- and LCA+-antigen-presenting cells, the intestinal mesentery can be classified as a primary lymphoid organ, thereby enriching the understanding of the immune system's organisation within the body.

CONCLUSIONS

Using peanut and lentil lectins, antigen-presenting cells in the small intestine mesentery of rats were detected for the first time using a lectin histochemistry method. Their functional activity was determined, and the ratio of antigen-presenting cells to the total number of lymphocytes, immunologically immature PNA+-lymphocytes, and SBA+-B-lymphocytes was studied under normal conditions and during the modelling of the adhesion process.

In the intact group of animals, PNA+-antigen-presenting cells in the mesentery of the small intestine are characterised by a star-shaped, elongated form, with projections that are nearly imperceptible. The number of identified cells was 2.74 ± 0.04 per 10,000 μm² of the studied area. LCA+-antigen-presenting cells, on the other hand, exhibit a more rounded shape, occasionally displaying three to four angles. Their petal-shaped nuclei and the sites of projection emergence are clearly visible. Under normal conditions, 2.05 ± 0.02 LCA+-antigen-presenting cells were found per unit area.

As adhesion processes progressed, the morphology of PNA+-antigen-presenting cells changed: becoming elongated, and slightly flattened with numerous winding processes, the length of which visually increased at each observation time point. The number of PNA+-antigen-presenting cells on the 21st day of the study increased to 3.5 ± 0.02 cells per unit area studied. LCA+-antigen-presenting cells acquired a crescent shape, polygonal with numerous punctate processes extending from the soma. On the 21st day of adhesion formation, their progressive increase to 5.8 ± 0.03 cells per unit area studied was observed. The topography of PNA+- and LCA+-antigen-presenting cells remained constant both in the norm and in the experiment.

The increase in the number of PNA+- and LCA+-antigen-presenting cells during adhesion formation indicates an increase in the immunoreactivity of lymphoid clusters associated with the serous membranes SALC and adipose tissue FALC. Against the background of the activation of antigen-presenting cells in the experiment, the total number of lymphocytes increases (ratio 1:4). The ratio of PNA+-immunologically immature lymphocytes and SBA+-lymphocytes also increases on the 21st day of observation, indicating the activation of the humoral link of lymphoid tissue associated with the serous membranes SALC and with adipose tissue FALC. There is a growth in the quantitative indicators of PNA+-lymphocytes and SBA+-lymphocytes against the background of an increase in antigen-presenting cells in the experiment. Analysis of the studied indicators made it possible to identify a relationship between the number of dendritic cells and PNA+- and SBA+-lymphocytes, which also complements the understanding of the mechanism of functioning of the local link of innate immunity. Prospects for further research include studying the features of the morphology and variation in the number of lymphocytes in the small intestine mesentery, as well as the features of different types of collagen fibres using a lectin histochemistry method.

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CONFLICT OF INTEREST

None.

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Дослідження антигенпрезентуючих клітин в бриж кишки в нормі і при спайковому процесі

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Анотація. Питання морфології і топографії дендритних клітин брижі тонкої кишки, їх кількість, наявність у нормі та при прогресуючих спайкових процесах вивчені недостатньо і постають актуальним питанням імуноморфології. Метою роботи було виявлення і визначення функціональної активності антигенпрезентуючих клітин методом лектинової гістохімії за допомогою лектинів арахісу та сочевиці у нормі та при спайкових процесах. Перелік використаних методів: морфометричний, лектингістохімічний, статистичний. Вперше за допомогою лектинової гістохімії із використанням лектинів сочевиці і сої виявлено функціонально активні та імунологічно незрілі антигенпрезентуючі клітини в структурі лімфоїдних кластерів брижі тонкої кишки. Встановлено закономірність між прогресуванням процесів спайкоутворення та кількістю антигенпрезентуючих клітин. Виявлено кореляційні зв'язки між дендритними клітинами та кількістю імунологічно незрілих лімфоцитів і В-лімфоцитів, що поглибило уявлення про функціональні механізми локальної ланки вродженого імунітету. Проаналізовано тенденцію зростання імунологічно незрілих лімфоцитів і В-лімфоцитів на тлі збільшення антигенпрезентуючих клітин. Результати показали, що активація дендритних клітин в тканинах брижі викликає збільшення імунологічно незрілих лімфоцитів, з яких в подальшому походять В-лімфоцити і ініціюють місцеву імунну відповідь. Підвищення частоти виявлення PNA+- і LCA+- антигенпрезентуючих клітин вказує на підвищену імунореактивність лімфоїдних кластерів. Дане дослідження розподілу антигенпрезентуючих клітин доповнює розуміння структури лімфоїдої тканини, пов'язаної з серозними оболонками, а також жироасоційованих лімфоїдних скупчень, і підкреслює зв'язок між вродженим і адаптивним імунітетом в черевній порожнині

Ключові слова: очеревина; дендритні клітини; імунітет; лектини; щури; лімфоцит; гістологічні зміни

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Interrelation of plasma haemostasis and heart rate variability in patients with chronic coronary syndrome in combination with COVID-19

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Abstract. The aim of the study was to identify the relationship between activated partial thromboplastin time, prothrombin time, fibrinogen, D-dimer and indicators of N-N interval deviations, heart rate, on the one hand, and to identify the relationship between parasympathetic and sympathetic heart rate activity and dynamic blood viscosity, on the other hand. The COVID-19 pathogen affects the functioning of the parasympathetic and sympathetic nervous systems, which also changes the heart rate. To study this process, a group of 10 patients with chronic coronary syndrome in combination with COVID-19 without comorbidities aged 35-48 years was observed in a hospital. To study this relationship, plasma haemostasis parameters (activated partial thromboplastin time, prothrombin time, fibrinogen, D-dimer) and heart rate variability were taken at the time of admission to the hospital and after discharge from the hospital. A direct correlation between the indicators was found: in patients 1 and 4, at the time of admission to the hospital, there was an increase in activated partial thromboplastin time, prothrombin time, D-dimer and a decrease in fibrinogen, which coincides with an increase in heart rate, 5-10 minute and long-term deviation of the N-N segments. That is, changes in blood plasma affect the rhythm of the heart already at the onset of COVID-19 in combination with chronic coronary syndrome. Patients 1 and 4 had an increase in D-dimer at the time of discharge from the hospital, which coincided with an increase in heart rate. Patients require further follow-up, as these are signs of a cautious prognosis. All other plasma haemostasis parameters are normal in all patients, with minor changes. It is necessary to monitor plasma haemostasis and heart rate variability to adjust treatment during hospitalization of patients with chronic coronary syndrome in combination with COVID-19 and after discharge from hospital

Keywords: activated partial thromboplastin time; prothrombin time; fibrinogen; D-dimer; N-N interval; parasympathetic-sympathetic activity

INTRODUCTION

Almost immediately after studying the pathogenesis of COVID-19, it became clear that it is more complex than just viral pneumonia and acute respiratory distress syndrome [1-3]. The relevance of studying the impact of this infection on the cardiovascular system is based on the fact that the "cytokine storm" caused by uncontrolled Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and the release of pro-inflammatory cytokines causes damage to many organs, including the heart. Another mechanism that causes cardiovascular manifestations is discoagulation and thromboembolic circumstances. The most common comorbidities were found in critically ill patients treated in intensive care units. The mechanism of chronic coronary syndrome (CCS) in patients with COVID-19 is not known for certain. It is assumed that it can be a spasm of the coronary arteries, the formation of microthrombi on the background of systemic inflammation or rupture of an atherosclerotic plaque.

That is, coronary thrombosis caused by endothelial dysfunction is a common process in COVID-19. This is not

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a theory, but a scientific axiom, and is an urgent problem of modern COVID-19 therapy. L. Chen *et al.* [4] documented cases where people who did not have cardiovascular disease at all (or had it latently) went to the hospital because of cardiovascular symptoms and were later diagnosed with COVID-19.

Thrombosis in COVID-19 has two possible origins. The first is that the virus damages the endothelium (the inner surface of blood vessels). In response to the invasion of the virus, pro-inflammatory proteins are produced on the endothelium, and the process of thrombosis begins. The second version of thrombus formation is associated with the effect of the virus on the immune system. A distinctive feature of SARS-CoV-2 is that it provokes a strong immune response. If the body cannot cope with the virus quickly, a so-called cytokine storm occurs. This is a complete "disorientation" of the immune system, when macrophages, the cells that protect the body, give a hyperresponse – they increase the synthesis of cytokines. This is followed by a whole cascade of reactions that leads to the production of substances that activate platelet and plasma haemostasis, and pathological thrombosis can begin even in intact vessels. Despite the possibility of developing CCS in SARS-CoV-2 infected individuals, the number of hospitalised patients with CCS has significantly decreased during the COVID-19 outbreak. According to M. Chung *et al.* [5] and E. Driggin *et al.* [6], it decreased by 40-50% in some countries.

The treatment of ST-segment elevation CCS in patients with COVID-19 should not differ from uninfected patients, and testing for SARS-CoV-2 should not delay revascularization. In turn, the management of patients with non-ST-segment elevation CCS should be based on risk stratification (very high, high, moderate, and low). Thus, patients with very high risk (criteria – unstable haemodynamics or cardiogenic shock; chest pain resistant to drug therapy; cardiac arrest or life-threatening rhythm disturbances; mechanical complications; acute heart failure and ST-segment elevation) should receive urgent invasive care. The exact mechanism of discoagulation in COVID-19 patients is not known. One hypothesis is that a severe inflammatory response and endothelial damage may have a prothrombotic effect. Also, blood stasis and immobilization of critically ill patients contribute to thrombosis. It is also worth noting the interaction of many drugs used to treat patients with COVID-19. For example, the combination of antiviral drugs lopinavir-ritonavir is metabolised through cytochrome P-450 3A4, which is also used to metabolise anticoagulants and antiplatelet agents. Consequently, the use of these drugs in the treatment may reduce the effectiveness of antithrombotic therapy. Finally, the amount of viral load in SARS-CoV-2 infection correlates with the severity of the disease, with higher viral loads at presentation correlating with the worst outcomes. The effect of SARS-CoV-2 on the heart has many manifestations, which are generally manifested by endothelial cell dysfunction. This causes changes in blood density, the formation, or destruction of blood clots, narrowing of the vessel span (including coronary vessels) and even destruction of the vessel structure.

Cardiovascular disease can occur in a healthy person in the post-COVID period, chronic, or mild cardiovascular disease becomes more severe during inpatient treatment for COVID-19, and the presence of any cardiovascular disease is a negative element in predicting the course of COVID-19. All of these theses are presented in the scientific articles by O. Golubovska [1] and M. Ackermann *et al.* [2].

R. Esmel-Vilomara *et al.* [7] and S.C. Fang *et al.* [8] point out the potential importance of direct viral toxicity in the pathogenesis of COVID-19 infections. The pathogenic effect of COVID-19 on the lungs causes an ischaemic effect, and in combination with the effect on the coronary vessels (compilation with ACE2), it increases the likelihood of myocardial infarction.

The complex interrelationships of the simultaneous effects of SARS-CoV-2 on the nervous system (which affects heart rate), the respiratory system (which also affects heart rate and plasma haemostasis), blood plasma levels (which changes the functioning of coronary vessels) and the vascular system (which affects plasma haemostasis). That is, plasma haemostasis and heart rate form the basis of this pathogenic effect. Thus, the aim of the study was to prove the direct mutual influence of changes in the two most important elements of the cardiovascular system: plasma haemostasis and heart rate. Thus, the tasks for achieving this goal are to study the theoretical basis of the problem under study; to identify the relationship between heart rate (HR), mean daily heart rate variability (SDANN), mean heart rate variability index (SDNN-i) and activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinoge, D-dimer; to identify the relationship between the low-frequency component of heart rate variability (LF), the power of heart rate oscillations in the high-frequency range (HF) and dynamic blood viscosity.

LITERATURE REVIEW

A number of studies have closely linked coronary pathophysiological phenomena to the course of COVID-19. For example, M. Ackermann *et al.* [2] noted direct damage to the vascular endothelium by the COVID-19 virus in the deceased; Z. Varga *et al.* [9] describe a series of cases of 3 patients with SARS-CoV-2 infection, where they demonstrated damage to the capillary endothelium by the virus with the development of endotheliitis in organs such as the intestines, lungs, and kidneys; O. Golubovska [1] studied post-COVID syndrome. According to her, endotheliitis explains systemic microcirculatory disorders and their clinical consequences in patients with COVID-19. Obviously, similar processes can occur in coronary vessels.

L. Chen *et al.* [4] and M. Hoffmann *et al.* [10] went even further in their studies when they examined the importance of angiotensin-converting enzyme 2 (ACE2). These studies are interesting because they proposed and confirmed the mechanism of pathogenesis by which it contributes to SARS-CoV-2-associated myocarditis, SARS-CoV-2 infects myocardial cells that express ACE2. These two pathological links (ACE2 expression and myocardial damage) mutually influence each other and create a pathophysiological vicious circle. Studying the mechanism of SARS-CoV-2 impact, M. Vaduganathan *et al.* [11] noted the importance of ACE2 penetration and its expression inhibition in the pathogenesis of SARS-CoV-2-associated myocarditis. This leads to a decrease in angiotensin absorption.

The impact of SARS-CoV-2 on heart rhythm has been observed since the first days of studying this pathology. D. Wang *et al.* [12] note that one of the first reports on

COVID-19 infected patients in Wuhan indicated that 46% of patients had some kind of comorbidity. The most common were hypertension (31%), cardiovascular disease (15%), and diabetes mellitus (10%). The trend was confirmed by further studies. COVID-19 infection can cause acute coronary syndrome. Thus, in a series of 18 patients with COVID-19 with ST-segment elevation on electrocardiography and suspected myocardial infarction, 5 patients required percutaneous coronary intervention. Observations by G.G. Stefanini *et al.* [13] showed that about 60% of patients infected with SARS-CoV-2 and ST-segment elevation had obstructive coronary disease and indications for revascularization. In 24 out of 28 patients in this series, the primary diagnosis was acute coronary syndrome, thus being the main manifestation of COVID-19. The problem is exacerbated by the fact that the development of ST-segment elevation and non-ST-segment elevation heart disease with the onset of heart pain may seem insignificant to a patient compared to the risk of going to the hospital during a pandemic, even if they already have undiagnosed COVID-19. This has led, for example, to the mandatory testing for COVID-19 for all patients with signs of SARS-CoV-2-associated myocarditis in Hong Kong.

CCS becomes acute after contracting COVID-19. Myocardial damage, defined as an increase in cardiac biomarkers or changes in electrocardiography, is observed in 5-20% of patients. Myocardial damage was most commonly observed in patients with severe disease treated in intensive care units and was associated with poorer outcomes and mortality. Another mechanism that causes cardiovascular manifestations is discoagulation and thromboembolic circumstances.

In their works, E. Driggin *et al.* [6] and N. Tang *et al.* [14] note a number of pathophysiological phenomena in patients with SARS-CoV-2 infection that sometimes act together and contradict each other according to pathophysiological logic: endothelial inflammation, increased coagulation and disseminated intravascular coagulation (DIC), thrombosis, and ischaemia. The mechanism of myocardial damage caused by SARS-CoV-2 is not fully understood, but it may be caused by systemic inflammation or direct infection of cardiomyocytes.

Deep vein thrombosis and pulmonary embolism are common complications in critically ill patients with COVID-19. Thus, according to autopsy data, deep vein thrombosis was detected in 58% and pulmonary embolism in 33% of patients who were not diagnosed with venous thrombosis during life. According to Y.D. Gao *et al.* [15] and J.M. Grégoire *et al.* [16], arterial thrombosis is also common in SARS-CoV-2 infected patients.

In addition, the presence of coronary artery disease, heart failure, arrhythmias, chronic obstructive pulmonary disease, age over 65 years and smoking in patients with COVID-19 are independent risk factors for in-hospital mortality. The impact of SARS-CoV-2 on the hypothalamus-pituitary-adrenal axis and the autonomic nervous system (ANS) should be considered separately, as its disorders are clinically manifested by changes in heart rate variability (HRV) and pathophysiologically contribute to cardiac death. This is stated in the works of K. Lundstrom *et al.* [17], S. Mandal *et al.* [18], and C. Minguito-Carazo *et al.* [19].

X. Yang *et al.* [20], X.W. He *et al.* [21], and Y.Y. Zheng *et al.* [22] note in their works that nine reports reported the association of acute heart injury with death, as well as dynamic changes in cardiac biomarkers during hospitalization. Scientists have noted a link between clinical symptoms of heart disease at the onset of the disease and the course of COVID-19. S.L. Harrison *et al.* [23], G. Hindricks *et al.* [24], and Q. Husain *et al.* [25] pointed out that heart disease progresses during the disease and can even occur in people who did not have heart disease before the disease. Thus, the review concluded that endotheliitis is the cause of cardiac pathologies in COVID-19, which causes the deterioration of both healthy hearts and hearts with chronic heart failure.

MATERIALS AND METHODS

The study was conducted at Bogomolets National Medical University. To confirm the claim that cardiovascular functioning is directly related to the course of COVID-19, 10 patients with CCS in combination with COVID-19 were monitored throughout their hospital treatment. The study continued during the patients' hospital stay. Comparative statistical analysis was used without the use of methods to assess the significance of changes.

Patients with mild disease who are not at risk of developing complications of COVID-19 are recommended to be treated on an outpatient basis (at home), but the selected patients had CCS and therefore received inpatient treatment. As can be seen from Table 1, the patients did not have all the factors that could affect the outcome of COVID-19: overweight, comorbidities (except for CCS), bad habits (except for patients 1, 4, 6), age (the oldest patient was 7-48 years old). Thus, a homogeneous group of 10 people with CCS diagnosed before COVID-19 infection was obtained.

Table 1. Personal data of patients

Patient	Age	Sex	Weight, kg	Height, cm
1	40	Female	85	178
2	35	Female	70	169
3	38	Male	69	160
4	32	Male	74	168
5	39	Female	73	162
6	35	Male	70	163
7	48	Male	69	162
8	45	Female	80	170
9	37	Male	74	175
10	35	Male	71	174

Source: compiled by the author

All parameters for the study were obtained twice: on the first day of hospitalization and before discharge. The most informative indicators of plasma haemostasis are APTT, PT, fibrinogen, and D-dimer. To study the changes in these parameters in patients with CCS in combination with COVID-19, the values at baseline, at the onset of the disease, and after recovery (or death) were taken. Before taking venous blood for the study, the patients were asked about the use of anticoagulants. None of the patients were taking such drugs. All parameters were determined using an automatic blood coagulation analyser Coagulometer K 3002 OPTIS (KSELMED, Poland). The data on physiological correlates of HRV parameters presented in Table 2 can be used to interpret the results of HRV analysis.

Table 2. Interpretation of HRV analysis results

Indicator	Definition	Nature
Temporal indicators		
SDANN	Standard deviation of SDNN averages from 5 (10) minute segments for medium duration, multi-hour or 24-hour recordings	Humoral regulation, activity of central oscillators
SDNN-i	Standard deviation of N-N intervals	Sympatho-parasympathetic modulation
Spectral characteristics		
LF	Power in the very low frequency range (0.04-0.15 Hz)	Sympatho-parasympathetic modulation of baroreflex nature
HF	Power in the very low frequency range (0.04-0.15 Hz)	Parasympathetic activity

Source: created by the author based on [23]

HRV and plasma haemostasis parameters were compared twice during the course of the disease: at the beginning of the disease and after its completion. HRV was studied using appropriate software (ECG-pro®Holter, IMESS, Ukraine). The study of plasma haemostasis parameters was performed on the first day of hospital stay. A coagulometer K 3002 OPTIC (KSELMED, Poland) was used to determine the dynamic blood viscosity. All patients received full information about the study, test results, and conclusions and prognoses in accordance with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [26]. This does not affect the results of the study and does not contradict the 2008 Declaration.

RESULTS AND DISCUSSION

The criteria for selecting patients for the study resulted in a fairly homogeneous group of patients. This is confirmed by the number of days of treatment (Table 3).

Table 3. Number of days of treatment

Patient	Number of days of treatment
1	15
2	10
3	11
4	15
5	10
6	11
7	11
8	12
9	12
10	11

Source: compiled by the author

All of the above leads to the conclusion that the average treatment duration was 13 days, which corresponds to the duration of treatment for mild COVID-19. The presence of a diagnosis of COVID-19 to affect plasma haemostasis on the first day of inpatient treatment meant that patients had passed the first (direct infection with the virus, the beginning of a pathophysiological chain reaction manifested by infection of immunocompetent cells of non-specific immune defence), second (excessive production of proinflammatory cytokines) and third (vascular endothelial damage, first in the lungs, then in other vessels, endotheliitis) stages of COVID-19 pathogenesis.

The third stage is of greatest importance for plasma haemostasis parameters because it was at this stage that patients were admitted to the hospital. It is at this stage (depending on the severity of the disease) that changes occur that lead, against the background of the depletion of the anticoagulation system due to endothelial destruction, to a sharp change in plasma haemostasis due to the entry of tissue thromboplastin into the bloodstream. At the same time, the natural fibrinolysis system could not cope with such a load. These two factors (decreased fibrinolysis and anticoagulation function) could lead (in the long run) to thrombosis of the heart's microvasculature. As a consequence, the impaired blood supply to the heart should certainly lead to changes in the heart rhythm. It should be noted that clinical manifestations of COVID-19 usually appear five days after infection. Thus, at the time of the COVID-19 diagnosis, plasma haemostasis parameters are presented in Table 4.

Table 4. Plasma haemostasis parameters on admission to the hospital

Patient	APTT		PT		Fibrinogen		D-dimer	
		Norm		Norm		Norm		Norm
1	42 s	30-40 s	19 s	11-18 s	1.9 g/L	2-4 g/L	0.6 mcg FEU/mL	0-0.55 mcg FEU/mL
2	40 s		18 s		2 g/L		0.5 mcg FEU/mL	
3	40 s		18 s		2 g/L		0.5 mcg FEU/mL	
4	42 s		19 s		1.9 g/L		0.6 mcg FEU/mL	
5	40 s		18 s		2.2 g/L		0.5 mcg FEU/mL	
6	40 s		18 s		3 g/L		0.5 mcg FEU/mL	
7	40 s		18 s		3 g/L		0.5 mcg FEU/mL	
8	40 s		18 s		2.2 g/L		0.5 mcg FEU/mL	
9	40 s		18 s		3 g/L		0.5 mcg FEU/mL	
10	40 s		18 s		2.4 g/L		0.5 mcg FEU/mL	

Source: compiled by the author

In severe cases of COVID-19, the massive entry of tissue thromboplastin into the vascular bed and the formation of a pro-convertin leads to significant changes in plasma haemostasis at the onset of the disease. In addition, the very concept of "onset of COVID-19" was subjective, as patients (voluntarily) might not immediately be admitted to the hospital, so the first day of inpatient treatment could differ in terms of plasma haemostasis due to a different number of days after infection. The table shows that patients do not differ significantly in terms of plasma haemostasis, so patients 1-10 were admitted to the hospital at approximately the same time of infection. In addition, it is worth not forgetting about the coagulation cascade that occurs as a result of the pathophysiological link due to the entry of tissue thromboplastin into the vessels and the activation of the Hagemann factor. According to Table 4, it can be concluded that at this stage, patients do not have severe pathological changes in plasma haemostasis.

Low APTT is a symptom of hypercoagulation. In this case, in patients 1 and 4, an elevated APTT may occur due to the initial stage of DIC syndrome. In most cases, anticoagulants are prescribed during the treatment of patients with COVID-19. Monitoring of such parameters as APTT, PT and fibrinogen allows for a prompt response to changes in the blood condition during inpatient treatment of COVID-19, and these tests are ordered immediately upon admission to the hospital. In this case, none of the patients received anticoagulants for both prophylactic and therapeutic purposes. It is recommended not to prescribe them due to low values, and to monitor the dynamics after discharge.

The PT indicates how long it takes for a fibrin clot to form in the blood serum. Fibrinogen (plasma fibrin) – its elevated level indicates inflammation in the body, a fibrin precursor protein that forms an insoluble clot. In the study, fibrin is at the lower end of the normal range, except for patients 1 and 4, who have lower levels.

The reasons for the decrease in fibrinogen can be severe liver damage (the organ where it is synthesised), test errors (when fibrin breakdown products in the blood plasma give a false result) or the DIC syndrome. In fact, there are more causes, including severe conditions of blood loss or shock, hereditary and gynaecological diseases, and cancer. All these causes were eliminated during the history taking. And the presence of elevated D-dimer in conjunction with a decrease in fibrinogen in patients 1 and 4 allows us to confidently conclude that the decrease in fibrinogen is associated with DIC. The etiopathogenesis of DIC syndrome is a generalised activation of blood coagulation, which can occur in parallel with the activation or inhibition of the fibrinolytic system. Microthrombi disrupt the blood supply to the coronary vessels, causing functional failure, which leads to changes in heart rate (especially in the context of pulmonary pathogenesis in COVID-19).

It is still unclear how SARS-CoV-2 activates the coagulation cascade. These questions have not been finally resolved in the 2020-2023 studies. M. Parohan *et al.* [27], and A.A. Rabaan *et al*. [28] note that mild COVID-19, the absence of bacterial sepsis and DIC syndrome result in a lower degree of prolongation of APTT and PT, and the presence of severe COVID-19 and other components on the contrary.

It should also be noted that the study by A. Silverio *et al.* [29] suggest that the coagulopathy observed in patients with severe COVID-19 is a mixture of localised pulmonary thrombotic microangiopathy and low-grade DIC. Assessment of the prognostic ability of haematological parameters yields mixed results. Significantly and prolonged elevated PT and APTT are independent predictors of mortality. H. Keski [31] notes that the frequency of abnormal haematological coagulation parameters increased with the severity of COVID-19. The D-dimer is directly correlated with COVID-19 mortality: the higher the D-dimer, the higher the likelihood of death. H. Keski [31] noted an increase in D-dimer in groups with acute respiratory distress syndrome and in a subgroup of patients with mortality. The increase in D-dimer concentration is primarily associated with the formation of blood clots of various sizes and health risks. Thrombi formed in the coronary and nervous system vessels pose the greatest threat. Thus, at the time of admission to the hospital, patients with CCS in combination with COVID-19 had an increase in APTT, PT and D-dimer in patients 1 and 4. In other patients, plasma haemostasis parameters were higher than normal. These data indicate the presence of inflammatory processes in all patients, processes at risk of a "red thrombus".

The increase in D-dimer and the presence of a smoking habit in patients 1 and 4 allows us to make a cautious prognosis. In general, according to the data obtained, no more than 25% of patients with an elevated D-dimer by 0.1-0.5 μm, an increase in APTT by no more than 5 seconds and PT by 3, and fibrinogen at the lower limit of normal in most cases correspond to a mild form of COVID-19.

In viral infections, the coagulation system is activated to protect the host, namely, to limit the spread of pathogens. Initially, an adaptive plasma haemostasis response occurs, which is associated with a systemic inflammatory response. As a result of increased inflammatory activity, the fibrinogen content increases significantly, and thrombin is produced. The studies on fibrinogen contradict this, so they were conducted after this adaptive reaction, when the body's plasma resource is reduced (Table 5).

Table 5. HRV in patients with CCS in combination with COVID-19 on admission to hospital

Patient	Indicators											
	HR, bpm		SDNN, ms		SDANN, ms		SDNNi, ms		LF, ms²/Hz		HF, ms²/Hz	
		Norm		Norm		Norm		Norm		Norm		Norm
1	102	60-90	89	51.6±1.7	58	77.5±3.8	60	51.1±1.8	2,500	710-770	2,670	386-411
2	85		75		50		51		1,060		1,106	
3	85		67		44		50		1,060		1,800	
4	102		89		58		60		2,500		2,670	
5	89		80		50		52		2,100		2,200	
6	90		80		44		51		2,200		2,400	
7	89		77		50		52		2,200		2,000	
8	90		78		50		50		1,500		2,200	
9	90		80		44		51		1,500		2,300	
10	90		80		48		50		1,500		2,340	

Source: compiled by the author

In fact, the HRV assessment also evaluates the functioning of the ANS. Currently, with mild COVID-19 on the first day of hospital treatment, the impact of the virus on the ANS was minimal. However, after treatment of the acute stage of COVID-19, nervous disorders of the ANS may develop due to hypoxic injury from the direct impact of the coronavirus on the respiratory and cardiovascular centres of the medulla oblongata and, as a result, HRV disorders. Conversely, high HRV stability indicates an overstrain of the ANS. HRV is an indicator of cardiovascular homeostasis and a very convenient tool for assessing stress resistance.

HR always responds to the needs of the body and a decrease in HR at the onset of the disease is a negative prognostic factor for the course of COVID-19, especially if patients already have CCS. At the same time, heart rate at the beginning of the disease is not informative. In practice, individual health characteristics have proven that a person can have a heart rate of less than 60 beats per minute or more than 100 beats per minute throughout their life, but they will feel fine [22]. More valuable information can be obtained by comparing the heart rate on the first day of inpatient treatment and after discharge. Then changes were visible for each individual patient. A similar principle exists in the analysis of HRV temporal and spectral parameters.

Despite the known negative impact of COVID-19 on the prognosis of patients with cardiovascular disease, there is currently a need to supplement the understanding of the pathophysiology of cardiovascular damage in SARS-CoV-2 infection, in particular, by studying changes and interrelationships in plasma haemostasis and HRV in patients with concomitant CCS (Table 6).

Table 6. Indicators of plasma haemostasis after discharge from hospital

Patient	APTT		PT		Fibrinogen		D-dimer	
		Norm		Norm		Norm		Norm
1	40 s	30-40 s	18 s	11-18 s	2 g/L	2-4 g/L	1 mcg FEU/mL	0-0.55 mcg FEU/mL
2	38 s		18 s		2 g/L		0.5 mcg FEU/mL	
3	37 s		18 s		2 g/L		0.5 mcg FEU/mL	
4	40 s		16 s		2 g/L		1 mcg FEU/mL	
5	38 s		18 s		2.2 g/L		0.5 mcg FEU/mL	
6	38 s		18 s		3 g/L		0.5 mcg FEU/mL	
7	37 s		18 s		3 g/L		0.5 mcg FEU/mL	
8	36 s		18 s		2.2 g/L		0.5 mcg FEU/mL	
9	38 s		18 s		3 g/L		0.5 mcg FEU/mL	
10	37 s		18 s		2.4 g/L		0.5 mcg FEU/mL	

Source: compiled by the author

Post-acute symptoms can occur in almost half of patients with COVID-19, so the study of HRV in the range of dynamic changes during the treatment of patients with CCS in combination with COVID-19 has a number of goals: diagnosis of heart disease, analysis of the activity of the ANS, and implementation of the stress response. Thus, the most pronounced increase in HRV was observed in patients 1 and 4 at the time of admission to the hospital. In patients 1 and 4, at the time of admission to the hospital, there was an increase in APTT, PT, D-dimer and a decrease in fibrinogen, which coincided with an increase in heart rate, 5-10 minute and long-term deviation of the N-N

segments. That is, changes in blood plasma affect the rhythm of the heart already at the onset of COVID-19 in combination with CCS. Other patients have normal plasma haemostasis and increased HRV compared to the norm. However, the increased HRV values can be explained by the fact that patients with CCS and normal HRV values are not relevant for them.

Among the patients, an increase in D-dimer of more than two norms (1 ng/mL) was determined in 24% of cases. The level of fibrinogen and other plasma haemostatic parameters did not exceed the normal range. Analysis of haemostatic parameters showed neither hypercoagulable tendencies nor signs of consumption. Indicators that are commonly observed in coronavirus infection, such as fibrinogen levels (hyper- or hypofibrinogenemia), reached normal values. During the acute phase of coronavirus, microthrombi with viral particles are formed. And when the body begins to fight these blood clots and dissolve them, the virus is released and provokes inflammation again. There is little information in scientific sources about blood counts in patients after discharge. S. Mandal *et al.* [18] noted an increase in D-dimer in one-third of patients (Table 7).

Table 7. HRV in patients with CCS in combination with COVID-19 after hospital discharge

Patient	Indicators											
	HR, bpm		SDNN, ms		SDANN, ms		SDNNi, ms		LF, ms²/Hz		HF, ms²/Hz	
		Norm		Norm		Norm		Norm		Norm	Norm	
1	112	60-90	88	51.6±1.7	58	77.5±3.8	38	51.1±1.8	2,500	710-770	2,670	386-411
2	89		75		50		39		1,060		1,106	
3	88		67		44		37		1,060		1,800	
4	112		89		56		38		2,500		2,670	
5	90		80		50		37		2,100		2,200	
6	91		80		44		39		2,200		2,400	
7	90		77		50		38		2,200		2,000	
8	90		78		50		37		1,500		2,200	
9	90		80		44		39		1,500		2,300	
10	92		80		48		38		1,500		2,340	

Source: compiled by the author

Resting heart rate in people with coronavirus was higher than normal. This trend may continue for some time in the post-COVID phase. A decrease in HF gives a poor prognosis for recovery from COVID-19 and the possibility of post-COVID complications. The fact that this indicator has hardly changed in patients provides a positive prognostic argument. HRV can also be assessed after discharge from the hospital. During a seemingly stable period when clinical symptoms of COVID-19 have almost disappeared, autonomic imbalance may occur, which is reflected in a decrease in HRV. This may indicate a higher risk of transitioning to the acute stage of CCS in the first 30 days after COVID-19 infection. The baseline minimum, average daily and maximum HR were 85 ± 1.3, 91.2 ± 8.5 and 102 ± 17.6 min, respectively, without significant dynamics during the repeated study. The baseline values of the temporal indicators were: SDNN – 79.5 ± 9.5 ms, SDNNi – 42.1 ± 17.9 ms, SDANN – 49.6 ± 8.4 ms.

In the dynamics, there was a tendency to decrease SDNNi by 10.7% ($p < 0.1$). Other temporary indicators decreased slightly. At the baseline HRV assessment by the 'short section analysis' method, the number of patients with normal HRV was 5 (33.3%), moderately reduced HRV – 9 (60%), and sharply reduced HRV – 1 (6.7%). In the dynamics, the number of patients with normal HRV did not change, but the number of patients with severely reduced HRV increased by 3 (20%), ($p = 0.1$), 66.7% of patients with CCS in combination with COVID-19 14 days after the development of focal neurological symptoms have moderately and severely reduced HRV. The analysis of the initial state of HRV parameters and their dynamics during the hospital and post-hospital follow-up periods in patients with CCS in both groups revealed statistically significant differences ($p < 0.05$). In patients 1 and 4, at the time of discharge from the hospital, an increase in d-dimer was noted, which coincided with an increase in heart rate. Patients require further follow-up, as these are signs of a cautious prognosis. According to other indicators, plasma haemostasis in all patients is normal, and HRV changes are not significant.

Coronavirus infection initiates activation of the sympathetic nervous system, and therefore the use of β-blockers has a positive effect on the restoration of sympathetic-parasympathetic regulation. In this regard, it is advisable to use higher doses of β-blockers in patients with CCS who have had COVID-19 to restore the sympathetic-parasympathetic balance. Slower recovery and adaptation, on the one hand, and ANS imbalance, on the other hand, may contribute to the development of life-threatening arrhythmias and fatal outcome. In view of these features of the restoration of neurohumoral mechanisms of myocardial regulation, when choosing pharmacotherapy in the hospital and posthospital stages, improving its effectiveness, building rehabilitation programmes and predicting their effectiveness in patients with ACS who have had coronavirus infection, it is necessary to take into account the presence of a longer period of severe sympathicotonia.

An increase in blood and plasma viscosity is associated with a decrease in oxygenation that develops during coronavirus infection. Moreover, rheological parameters change in the subclinical phase of atherosclerosis, that is, HRV changes along with plasma haemostasis parameters already with the development of vascular risk factors. Thus, a slight expression of coronary atherosclerosis, which is simultaneously associated with changes in N-N intervals and a decrease in blood viscosity, is observed. This is particularly evident in patients 1 and 4.

Blood viscosity cannot be considered separately. A. Colantuoni *et al.* [32] generally consider fibrinogen to be the main factor in blood viscosity, and therefore all three diagnostic elements under study (coagulogram, blood viscosity, and HRV spectral parameters) are interdependent. According to the literature, an increase in blood viscosity in CCS in combination with COVID-19 is detected from the first day, and the severe form of this disease is associated with a complicated course. Changes in blood viscosity may be a result of an imbalance in neurohumoral regulation. This is confirmed by a number of sources that directly recommend the use of drugs that affect the ANS during the treatment of COVID-19 [27, 28]. Chronic heart failure combined with COVID-19 is more complex and associated with proinflammatory cytokines and neurometabolic imbalances that together affect cardiomyocyte function, but all negative pathogenic manifestations during the acute stage of the disease are still associated with endothelial dysfunction. Under the influence of this imbalance, vascular tone increases and blood moves more slowly through the vessels. This leads to changes in HRV, endothelial damage, and an increased likelihood of pathophysiological causes of blood clots. This was confirmed in a study that found a direct positive correlation between LF and blood viscosity at shear rates from 0.22 to 2.62 seconds. This was especially evident on the first day of hospitalization. The reason for this interaction is the negative effect of increased adrenergic activity with the formation of catecholamines on the dynamic blood viscosity.

CONCLUSIONS

It has been established that plasma haemostasis comprises several indicators that directly affect both heart rate and blood clot formation and the duration of treatment for COVID-19. These are coagulation parameters: APTT, PT, fibrinogen, D-dimer, which generally shows a direct correlation with the results and duration of treatment, and dynamic blood viscosity, which has shown a direct correlation with the sympathetic and parasympathetic components of cardiovascular regulation.

In the studied cases, a mild form of COVID-19 was dealt with, so the correlation of HRV and such indicators as APTT, PT, fibrinogen, and D-dimer was most informative at the onset of the disease. Here, 2 patients (i.e., 20%) of the study had the most pronounced symptoms of autonomic dysfunction in patients with CCS in terms of increased HR, 5-10 minute and long-term N-N segment deviation, and symptoms of plasma haemostasis changes such as increased APTT, PT, D-dimer, and decreased fibrinogen. These 2 patients had the longest number of days of hospital treatment and a 0.5 μg FEU/mL increase in D-dimer from the normal range. Thus, more pronounced pathological changes in HRV parameters and plasma haemostasis are directly related and affect the quality and duration of treatment of CCS in combination with COVID-19. Blood viscosity was particularly informative at the onset of the disease.

This study had a small practical research basis (only 10 patients) because the sample of patients with CCS in combination with COVID-19 without significant comorbidities is very difficult. Therefore, further research is needed because there are very few studies directly related to the treatment of CCS in combination with COVID-19.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Взаємозв'язок показників плазмового гемостазу та варіабельності серцевого ритму у хворих на хронічний коронарний синдром у поєднанні COVID-19

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Анотація. Метою дослідження було виявлення взаємозв'язку між показниками активованого часткового тромбопластинового часу, протромбінового часу, фібриногену, Д-дімеру та показниками відхилень N-N інтервалів, частоти серцевого ритму з одного боку і виявлення взаємозв'язку між показниками парасимпатичної та симпатичної активності серцевого ритму та динамічної в'язкості крові з другого боку. Збудник COVID-19 впливає на роботу парасимпатичної та симпатичної нервової системи, що також змінює серцевий ритм. Для вивчення цього процесу група з 10 пацієнтів із хронічним коронарним синдромом у поєднанні COVID-19 без супутніх захворювань у віці 35-48 років спостерігалась у стаціонарі. Для вивчення цього взаємозв'язку було взято показники плазмового гемостазу (активований частковий тромбопластиновий час, протромбіновий час, фібриноген, Д-дімер) та показники варіабельності серцевого ритму на момент надходження у стаціонар та після виписки зі стаціонару. Виявлений безпосередній зв'язок показників: у пацієнтів 1 та 4 на момент надходження у стаціонар відмічається збільшення активованого часткового тромбопластинового часу, протромбінового часу, Д-дімеру та зменшення фібриногену, це співпадає із підвищенням частоти серцевого ритму, 5-10 хвилинного та багаточасового відхилення сегментів N-N. Тобто зміниу плазмі крові впливають на ритм роботи серця вже на початку розвитку COVID-19 у поєднанні із хронічним коронарним синдромом. У пацієнтів 1 та 4 на момент виписки зі стаціонару відмічається збільшення Д-дімеру, це співпадає із підвищенням частоти серцевого ритму. Пацієнти потребують подальшого спостереження, оскільки це ознаки обережного прогнозу. Усі інші показники плазмового гемостазу у всіх пацієнтів у нормі, зміни незначні. Необхідно відстежувати показники плазмового гемостазу та варіабельності серцевого ритму для корекції лікування під час знаходження у стаціонарі пацієнтів із хронічним коронарним синдромом у поєднанні COVID-19 та після виписки зі стаціонару

Ключові слова: активований частковий тромбопластиновий час; протромбіновий час; фібриноген; Д-дімер; N-N інтервал; парасимпатична-симпатична активність

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Effectiveness of thrombolytic therapy in patients with severe COVID-19 and pulmonary embolism

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Abstract. Current research provides insufficient data on the use of thrombolytic therapy in the treatment of pulmonary embolism in patients with COVID-19. Existing studies present data on the efficacy of thrombolytic drug therapy for thrombotic complications in severe COVID-19. However, these studies either involve a very small number of observations or remain incomplete. This article aimed to assess systemic thrombolysis's effectiveness in intravenous alteplase administration in this pathology. The medical records of 92 patients were analysed. Patients were divided into four groups depending on the therapy administered. Patients in the first group had complications in the form of pulmonary embolism but did not require thrombolytic therapy. Treatment of patients in the first group consisted of prescribing low-molecular-weight heparin at a therapeutic dose. Patients in the second and third groups had pulmonary embolism in the context of COVID-19 and required thrombolytic therapy. The third group differed from the second in the presence of a thrombus in the right heart. Patients in the fourth group had complications in the form of pulmonary embolism, and required thrombolytic therapy, but did not receive it due to a lack of funds. Patients in the second and third groups were immediately treated with unfractionated heparin and alteplase. Thrombolysis was not performed in the fourth group. Mortality rates were studied according to the assigned group. It was established that the risk of death increased ($p < 0.001$) with increasing levels of D-dimer and decreased with increasing PaO2/FiO2 ($p < 0.001$). In the presence of a thrombus in the right heart chambers, the risk of death increased ($p = 0.002$), OR = 3.97 (95% CI 1.66-9.49). A trend towards reducing death risk with thrombolytic therapy was observed ($p = 0.052$). Data were summarised regarding the increased ($p = 0.009$) risk of death when thrombolytic therapy was delayed. Mortality in the fourth group was 100%. The obtained data indicate the significant effectiveness of thrombolytic therapy in the treatment of this pathology

Keywords: thrombolysis; acute respiratory distress syndrome; alteplase; unfractionated heparin

INTRODUCTION

Pulmonary embolism (PE) is a condition that cannot be successfully treated without therapy aimed at dissolving the thrombus. One of the characteristics of COVID-19 is the development of complications related to coagulation disorders, primarily hypercoagulation. According to Y. Wang *et al.* [1], hypercoagulation in COVID-19 patients may manifest through elevated levels of D-dimer, C-reactive protein, and ferritin, and is associated with increased mortality. The idea of using fibrinolytic agents in this group of patients is not new. Data from the ongoing clinical trial of Fibrinolytic therapy to treat ARDS in the setting of COVID-19 infection [2] suggest that fibrinolytic therapy in severe COVID-19 patients improves alveolar ventilation and reduces respiratory failure. This was a phase one clinical trial, where fibrinolytic therapy led to reduced mortality and improved oxygenation. According to the clinical study Tenecteplase in patients with COVID-19, the thrombolytic agent tenecteplase may improve outcomes in patients with severe COVID-19 [3]. The ongoing study Low-Dose Tenecteplase in COVID-19 Diagnosed with Pulmonary Embolism [4] continues to explore the role of this thrombolytic agent in severe COVID-19 cases. According to T. Iba *et*

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al. [5], coronavirus disease causes hypercoagulation with local thrombus formation. Z. Varga *et al.* [6] pointed to endothelial dysfunction and endothelitis as the cause of thromboembolic complications in patients with severe COVID-19. Theoretically, thrombolytics should be used in the treatment of such conditions.

J. Wang *et al.* [7] suggest that thrombolytic therapy may improve survival in critically ill COVID-19 patients. The authors describe their experience treating only three patients. All patients showed improvement after treatment with tissue plasminogen activator. All three patients noted a temporary improvement in respiratory status, and one patient had a sustained improvement. C.D. Barrett *et al.* [8] present the results of treating five COVID-19 patients with alteplase. All patients exhibited respiratory and clinical improvement. The authors concluded that further studies are necessary to determine the optimal regimen for thrombolytic therapy. The ongoing randomised trial by H.B. Moore *et al*. [9] provides data on the efficacy, safety, and dosage of alteplase in the COVID-19 patient population. H.D. Poor *et al.* [10] describe their experience with alteplase in the treatment of four patients with severe respiratory failure caused by severe COVID-19. They suggest that respiratory failure due to pulmonary thrombi in severe COVID-19 requires thrombolysis. According to J.M. Connors *et al.* [11], early thrombolytic therapy in patients with localised pulmonary thrombosis may be considered as a treatment for the uncontrolled coagulation cascade and the interplay between inflammation and coagulation mechanisms in COVID-19.

Thus, existing studies dedicated to investigating the use of thrombolysis in treating pulmonary embolism in severe COVID-19 patients indicate a positive effect of such therapy. However, these studies involve a very small number of clinical cases. All the aforementioned authors insist on the need for further research involving larger patient numbers. This study aimed to evaluate the effectiveness of systemic thrombolysis in providing emergency care to patients with PE against a background of severe COVID-19.

MATERIALS AND METHODS

In this retrospective study, the medical records of 92 patients with severe COVID-19 and PE who were treated in the intensive care unit of Kyiv City Hospital No. 4 from 1 January 2021 to 28 December 2021 (retrospective group) were reviewed. The inclusion criteria were as follows: laboratory-confirmed COVID-19, bilateral pneumonia on computed tomography, partial oxygen pressure in the blood below 60 mmHg when breathing ambient air, a D-dimer level above 0.7 mg/L, and a diagnosis of PE established by ultrasound and computed tomography. All patients underwent ultrasound scanning using the VOLUSON 730 EXPERT and VIVID 7 (GE, USA) systems. The criteria for PE were based on reduced RV output (the "60-60" sign) or reduced contractility of the free RV wall compared to its apex (McConnell's sign). The diagnosis was confirmed using computed tomographic pulmonary angiography when possible, depending on the patient's haemodynamic stability. Computed tomography was performed using a multi-slice Aquilion 64 CT scanner (Toshiba, Japan).

Based on diagnostic results, the patients were divided into two groups. The first group (n = 18) consisted of patients with low-risk and intermediate-low-risk PE, with a Pulmonary Embolism Severity Index (PESI) score ⩽85, corresponding to class I or II, and no signs of RV dysfunction or myocardial injury markers. Treatment for PE involved administering therapeutic doses of low-molecular-weight heparin. The second group (n = 29) included patients with intermediate-high-risk and high-risk PE without the presence of thrombi in the right heart chambers but with signs of RV dysfunction. Criteria for high-risk PE included shock, hypotension, or signs of RV overload (dysfunction), with a PESI score >85, corresponding to class III-V. RV dysfunction was identified by the presence of more than one of the following three signs: RV diastolic diameter (parasternal view) exceeding 30 mm or RV/left ventricular (LV) ratio >1; systolic flattening of the interventricular septum; or an acceleration time of less than 90 ms in the absence of RV hypertrophy. The third group (n = 29) comprised patients with intermediate-high-risk and high-risk PE combined with the presence of thrombi in the right atrium or RV.

The treatment of patients in the second and third groups involved immediate therapy with unfractionated heparin, adjusted based on activated partial thromboplastin time (70-120 seconds), and thrombolysis. Thrombolysis was performed using alteplase. The total dose of alteplase was 100 mg, administered over 2 hours [7]. Thrombolytic therapy was initiated as soon as possible but was most often started after the patient had acquired the necessary medication.

The fourth group (n = 16) consisted of patients with intermediate-high and high-risk PE for whom thrombolysis was indicated but was not performed due to the patient's inability to afford the cost of thrombolytic therapy. Treatment was provided using unfractionated heparin, with the dose adjusted according to the activated partial thromboplastin time (70-120 seconds).

Before initiating therapy, a range of markers characterising the patients' condition were assessed: ferritin levels (by quantitative immunoturbidimetric method) [12], interleukin-6 (IL-6) (by electrochemiluminescent immunoassay) [13], and C-reactive protein (CRP) (by solid-phase immunometric analysis) [14]. The levels of D-dimer [15] and procalcitonin (by immunochemical method with electrochemiluminescent detection) [16] were also measured. Additionally, the day of hospital admission following the onset of illness was recorded for all patients.

Based on the analysis of the coefficients from the four-factor model, the risk of mortality index (YR) was calculated using the following formula:

$$YR = -22{,}9 \times X_1 + 22{,}2 \times X_2 - 1{,}22 \times X_3 - 0.88 \times X_4 + 18{,}66, \quad (1)$$

where $X_1 = 1$ if thrombolysis was used and $X_1 = 0$ if thrombolysis was not used; $X_2 = 1$ in case of Overload and $X_2 = 0$ in case of no Overload; X_3 is the level of Leukocytes; X_4 is the value of PaO2/FiO2/10. The test based on the YR index allows for a highly accurate prediction of the risk of death. The sensitivity of the proposed test is 98% (95% CI 89.4%-99.9%), the specificity of the test is 71.4% (95% CI 55.4%-84.3%), +PV = 80.3% (95% CI 71.6%-86.8%), -PV = 96.8% (95% CI 81.0%-99.5%).

The study was approved by the Bioethics Committee of Kyiv City Clinical Hospital No. 4 [Protocol No. 54 dated 22 December 2020]. All research was conducted by the

fundamental provisions of the Council of Europe Convention on Human Rights and Biomedicine, in compliance with the World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects (with amendments) [17], and the Order of the Ministry of Health of Ukraine dated 23 September 2009 No. 690 [18]. As the study was retrospective in design, Ukrainian legislation did not require informed consent for the research.

As the distribution differed from normal according to the Shapiro-Wilk test, the median (Me) and interquartile range (QI-QIII) were calculated to characterise the quantitative indicators. The Mann-Whitney U test was used for comparisons between the two groups. For qualitative indicators, frequencies (%) were calculated, and Fisher's exact test was employed to compare the two groups. To quantitatively assess the degree of influence of factor variables on the risk of mortality, logistic regression modelling and analysis were utilised. The impact of factor variables was evaluated using odds ratios (OR), with 95% confidence intervals (CI) calculated. The analysis was conducted using MedCalc® statistical software version 20014. Two-tailed critical area criteria were applied, with a critical significance level set at $\alpha crit. = 0.05$.

RESULTS

The study was conducted from 1 January 2021 to 28 December 2021. The overall mortality rate in the intensive care unit was 28.6%, which was comparable to rates reported in other intensive care units globally [19]. Table 1 presents the risk of requiring mechanical ventilation and mortality in the studied groups. The highest risk of death and MV was observed in the fourth group of patients, where 100% were on MV and ultimately died. Mortality rates and the need for MV in the other groups differed significantly from those in the fourth group. The third group had the second-highest mortality and MV rates. The lowest risk of death and MV requirement was observed in the first and second groups.

Table 1. Risk of mechanical ventilation requirement and mortality

Indicator	Low-risk PE without thrombolysis (n = 18)	High-risk PE with thrombolysis (n = 29)	High-risk PE with thrombus in right heart, thrombolysis (n = 29)	High-risk PE with thrombus in right heart, no thrombolysis (n = 16)	p-value
Number of MV cases	7 (38.9%)*	15 (51.7%)*	16 (55.2%)*	16 (100%)	0.002
Number of deaths	7 (38.9%)*	11 (37.9%)*	16 (55.2%)*	16 (100%)	<0.001

Notes: comparisons were made using Fisher's exact test with Bonferroni correction; * – significant difference from the fourth group, $p < 0.05$
Source: provided by the author

To identify factors associated with the risk of mortality, logistic regression modelling was employed. Twelve indicators were analysed as risk factors: group assignment based on whether thrombolysis was performed (Group), age, day of thrombus detection (Day of detection), obesity, D-dimer, CRP, white blood cell count (Leukocytes), platelet count (Platelets), PaO2/FiO2 ratio (PaO2/FiO2), ferritin levels (Ferritin), thrombus in the right chamber, and right ventricular overload. Table 2 presents the results of this analysis.

Table 2. Analysis of mortality risk

Factor		Model coefficient, b ± m	Significance of coefficient deviation from 0, p	OR (95% CI)
Group	Thrombolysis No	Reference		
	Thrombolysis Yes	−0.88 ± 0.45	0.052	0.42 (0.17–1.01)
Age, per year		0.057 ± 0.020	**0.004**	**1.06 (1.02–1.10)**
Day of detection, per day		0.081 ± 0.036	**0.027**	**1.08 (1.01–1.16)**
Obesity	No	Reference		
	Yes	0.24 ± 0.48	0.619	–
D-dimer, per μg/mL		0.47 ± 0.13	**<0.001**	**1.60 (1.24–2.08)**
CRP, per 10 mg/L		0.01 ± 0.13	0.931	–
Leukocytes, per 10^9/L		−0.28 ± 0.16	0.132	–
Platelets, per 10^{10}/L		−0.04 ± 0.11	0.687	–
PaO2/FiO2, per 10 mmHg		−0.52 ± 0.12	**<0.001**	**0.59 (0.47–0.74)**
Ferritin, per 1 mg/L		0.74±0.58	0.199	–
Thrombus in the right chamber	No	Reference		
	Yes	1.38 ± 0.45	**0.002**	**3.97 (1.66–9.49)**
Right ventricular overload	No	Reference		
	Yes	0.78 ± 0.54	0.147	–

Notes: post hoc comparisons were conducted using Fisher's exact test
Source: provided by the author

In the univariate analysis, a trend towards a reduced risk of mortality was observed with thrombolytic therapy (p = 0.052) compared to patients who did not undergo thrombolysis. An increased risk of mortality was associated with advancing age (p = 0.004), with an odds ratio (OR) of 1.06 (95% CI 1.02-1.10) for each additional year. The risk of mortality also increased (p < 0.001) with rising D-dimer levels, OR = 1.60 (95% CI 1.24-2.08) per μg/mL. Conversely, for each 10 mmHg increase in PaO2/FiO2, the risk of mortality decreased (p < 0.001), OR = 0.59 (95% CI 0.47-0.74). The presence of a thrombus in the right chamber significantly raised the risk of mortality (p = 0.002), OR = 3.97 (95% CI 1.66-9.49) compared to patients without thrombi. To identify the set of factors associated with mortality risk in all patients (both those who did and did not undergo thrombolysis), independent variables were selected using multivariate logistic regression models. Four key risk factors were identified: Group, Leukocytes, PaO2/FiO2, and Right Ventricular Overload.

The analysis of the coefficients in the four-factor model suggests that in cases of RV overload, only thrombolysis can prevent a fatal outcome. A table can be constructed to illustrate changes in the risk of death depending on the value of the mortality risk index YR (Table 4).

Table 3. Analysis of mortality risk in the four-factor logistic regression model

Factor		Model coefficient, b ±m	Significance of coefficient deviation from 0, p	OR (95% CI)
Group	Thrombolysis No	Reference		
	Thrombolysis Yes	−22.9	**<0.001**	–
Leukocytes, per 10^9/L		−1.22 ± 0.38	**0.002**	**0.29 (0.14–0.63)**
PaO2/FiO2, per 10 mmHg		−0.88 ± 0.21	**<0.001**	**0.41 (0.27–0.63)**
Right ventricular overload	No	Reference		
	Yes	22.4	**<0.001**	–

Notes: the chi-squared test was used for comparison
Source: provided by the author

Table 4. Risk of death based on the mortality risk index YR

Mortality Risk Index YR	Risk of mortality
<=0	3.2%
0--2	50.0%
2--4	83.3%
>4	100.0%

Source: provided by the author

Next, data from only those patients who underwent thrombolysis (previously referred to as the "thrombolysis yes" group) are analysed. Ten risk factors were considered: age, day of thrombus detection (Day of detection), day of thrombolysis (Day of TL), obesity, D-dimer, CRP, leukocyte count (Leukocytes), platelet count (Platelets), respiratory index (PaO2/FiO2), ferritin levels (Ferritin), and presence of a thrombus in the right heart chamber. The results of the mortality risk analysis in univariate models are shown in Table 5.

Table 5. Analysis of mortality risk in univariate models

Factor		Model coefficient, b±m	Significance of coefficient deviation from 0, p	OR (95% CI)
Age, per year		0.042 ± 0.024	0.078	–
Day of detection, per day		0.042 ± 0.043	0.328	–
Day of thrombolysis, per day		0.55 ± 0.21	**0.009**	**1.73 (1.14–2.62)**
Obesity	No	Reference		
	Yes	0.16 ± 0.59	0.792	–
D-dimer, per μg/mL		0.36 ± 0.15	**0.021**	**1.43 (1.06–1.93)**
CRP, per 10 mg/L		−0.21 ± 0.17	0.200	–
Leukocytes, per 10^9/L		−0.56 ± 0.30	0.063	–
Platelets, per 10^{10}/L		−0.05 ± 0.13	0.710	–
PaO2/FiO2, per 10 mmHg		−0.57 ± 0.17	**0.001**	**0.56 (0.41–0.78)**
Ferritin, per 1 mg/L		−0.05 ± 0.69	0.937	–
Thrombus in the right chamber	No	Reference		
	Yes	0.70 ± 0.53	0.190	–

Notes: the chi-squared test was used for comparison
Source: provided by the author

In the univariate analysis, an increase in the risk of fatal outcomes (p = 0.009) was identified when thrombolysis was delayed, with an OR of 1.73 (95% CI 1.14–2.62). The critical threshold for the model was found to be TL_{crit} = 1 day; exceeding this period significantly increases the likelihood of a fatal outcome. Additionally, an elevated risk of mortality (p = 0.021) was observed with rising D-dimer levels, OR = 1.43 (95% CI 1.06–1.93) per μg/mL increase. The model identified a critical threshold for D-dimer of 5,844 ng/mL; surpassing this value predicts a higher probability of a fatal outcome. Conversely, an increase in PaO2/FiO2 levels was associated with a decreased risk of mortality (p = 0.001), OR = 0.56 (95% CI 0.41–0.78) for every 10 mm Hg. The critical threshold for PaO2/FiO2 was 144 mm Hg, and below this value, the model predicts a higher risk of mortality. To identify a set of factors associated with mortality risk, independent variables were selected using multivariate logistic regression models. Two key risk factors were identified: the day of thrombolysis (Day of TL) and the respiratory index (PaO2/FiO2). Table 6 presents the coefficient values for the model.

Table 6. Mortality risk analysis in the two-factor logistic regression model

Factor	Model coefficient, b ± m	Significance of coefficient deviation from 0, p	OR (95% CI)
Day of TL, per day	0.56 ± 0.26	**0.034**	**1.75 (1.04–2.93)**
PaO2/FiO2, per 10 mmHg	−0.55 ± 0.17	**0.001**	**0.58 (0.42–0.80)**

Notes: the chi-squared test was used for comparison
Source: provided by the author

In the multivariate analysis, a delay in thrombolysis was found to increase the risk of mortality (p = 0.034), with an OR of 1.75 (95% CI 1.04-2.93) per day (standardised for the PaO2/FiO2 ratio). An increase in the PaO2/FiO2 ratio was associated with a decrease in the risk of mortality (p = 0.001), OR=0.58 (95% CI 0.42-0.80) per 10 mm Hg (standardised for the Day of TL). When selecting the optimal threshold for predicting mortality (Y_{crit} > 0.3766), the proposed test showed a sensitivity of 88.9%, specificity of 67.7% (95% CI 48.6%-83.3%), +PV = 70.6% (95% CI 58.6%-80.3%), and -PV = 87.5% (95% CI 70.1%-95.4%). Critical thresholds for high mortality risk on specific days of thrombolysis, depending on the PaO2/FiO2 level, are presented in Table 7.

Table 7. Critical thresholds for high mortality risk based on PaO2/FiO2 levels by thrombolysis day

Day of thrombolysis	PaO2/FiO2 level indicative of mortality
Day 0	<132
Day 1	132-141
Day 2	142-152
Day 3	153-162
Day 4	⩾163

Source: provided by the author

Mortality rates among patient groups were influenced by the severity of PE risk and the treatment administered. Mortality rates in groups two and three showed almost no significant difference. Although the risk of death in the first group was lower, the use of thrombolysis in the second group offset this difference. Thrombi in one of the right chambers of the heart, combined with PE, were found in 489% of PE patients (45 patients), which is 2.7 times higher than the prevalence of right heart thrombi in non-COVID-related PE cases [13]. This is likely attributable to the presence of COVID-19. The presence of a thrombus in one of the right heart chambers worsened the prognosis, with mortality increasing by 1.46 times compared to patients without thrombi. Thrombolysis in patients with high-risk PE and a thrombus in the right heart chamber reduced mortality by 1.81 times.

In evaluating the overall results, it should be noted that the factors associated with a higher risk of mortality in patients were delays in thrombolysis, advanced age, elevated blood D-dimer levels above 5,844 ng/mL, a decrease in the PaO2/FiO2 index below 144 mmHg, and the presence of a thrombus in the right heart chambers. The factor that significantly reduced the risk of death across all study groups was the administration of thrombolytic therapy.

DISCUSSION

The role of coagulation disorders in the pathogenesis of COVID-19 is unequivocal. COVID-19 is a pronounced prothrombotic state [20]. The “cytokine storm” that occurs during the development of COVID-19 activates the coagulation cascade, leading to thrombosis. According to N. Tang *et al.* [21], widespread thrombus deposition disrupts blood supply, often leading to death. T. Iba *et al.* [22] reported that 71.4% of patients who died from COVID-19 were diagnosed with COVID-19-associated coagulopathy. H. Asakura *et al.* [23] suggest that PE is one of the complications of coagulopathy. M.B. Malas *et al.* [20] wrote that impaired coagulation, endothelial dysfunction, dehydration, and limited mobility contribute to a significantly increased risk of PE in COVID-19.

According to B. Mestre-Gómez *et al.* [24], mortality from COVID-19 is directly correlated with blood D-dimer levels. Studies of D-dimer in the examined patients showed a high prognostic value of the indicator, but low specificity of the test for diagnosing PE. According to S.C. Liao *et al.* [25], an increase in D-dimer levels above 700 ng/mL can

be characteristic of both PE and inflammatory syndrome. A decrease in D-dimer levels below 700 ng/mL unequivocally indicates that the patient does not have PE. According to F. De Cobelli *et al*. [26], blood D-dimer levels can increase up to 10,006 ng/mL in case of pulmonary embolism. According to P.K. Woodard [27], an increase in D-dimer above 5,000 ng/mL is a predictor of PE. According to the obtained data, the average D-dimer level in patients with COVID-19 and PE was 5,703.7 ng/mL.

According to M.B. Malas *et al.* [20], patients with hypercoagulability on the background of COVID-19 are at risk of new embolism. PE is accompanied by acute, but potentially reversible, right ventricular failure. Diagnosing PE is challenging due to its nonspecific clinical presentation. Early diagnosis is crucial as immediate treatment is highly effective. In cases of massive PE, urgent restoration of blood flow through thrombosed pulmonary arteries (PAs) is necessary, as suggested by S.V. Konstantinides *et al.* [28].

D.M. Dudzinski *et al.* [29] argue that there are two forms of PE, defined as central (main PA branch) and peripheral (segmental or subsegmental PA branch). According to D. Akdis *et al.* [30], in 4-19% of cases, thrombi in the right heart chambers can lead to PE.

S S.V. Konstantinides *et al.* [28] and D. Akdis *et al.* [30], who studied pulmonary vessel thromboses in the context of COVID-19, raised the question of whether pulmonary vessel thrombosis is a manifestation of recurrent thromboembolism resulting from the extension of primary thrombosis in the inferior vena cava system, or whether it is a primary local thrombosis due to endothelial injury. In other words, the question is where the thrombi form: in the inferior vena cava system, from where they then travel with the blood flow to the lungs, or in the pulmonary vessels themselves. There is pathogenetic evidence to support both theories.

The primary cause of hypercoagulation in COVID-19 is hypoxia. In hypoxic epithelial cells, a factor is produced, the activation of which stimulates the coagulation cascade and leads to the formation of microthrombi [31]. According to F. De Cobelli *et al*. [26], in addition to a possible direct cytopathic effect, the virus can induce a local cytokine-dependent inflammatory response. Viral replication causes cell infiltration, leading to the initiation of coagulation cascades, apoptosis of endothelial cells, and thrombosis of pulmonary vessels, as suggested by J. Helms *et al.* [32].

B. Mestre-Gómez *et al.* [24] reported that direct viral infection of endothelial cells develops in kidney and small intestine tissue. That is, primary thrombi in COVID-19 can form in peripheral vessels, from which they then travel with the blood flow to the lungs. According to the authors of this study, both theories regarding the presumed sites of thrombus formation are correct, i.e., thrombi form both in the inferior vena cava system and directly in the pulmonary vessels. Thrombi in one of the right heart chambers, detected by the study authors, either entered the heart from the inferior vena cava system or formed directly in the heart. They were not related to the pulmonary vessels.

The authors of the study found the prevalence of PE to be an interesting and variable aspect. As noted by E. Martínez Chamorro *et al.* [33], the reported incidence of PE in such patients varies from 0.7% to 57%. In a study by J. Poissy *et al.* [34], 20.6% of cases of PE were reported among 107 patients with severe COVID-19. According to E. Martínez Chamorro *et al.* [33], a multivariable meta-analysis showed a higher incidence of PE in patients with greater disease severity ($P < 0.001$). P. Kapała *et al.* [35] reported that the proportion of patients with acute PE was 23% in a subgroup of 100 patients with severe COVID-19. Simultaneously, pulmonary embolisms were detected in 78.6% of those with severe COVID-19. Y.J. Suh *et al.* [36] reported a prevalence of PE in COVID-19 patients of 16.5%. When several study characteristics were adjusted, the incidence of PE in patients who were critically ill and hospitalised in the intensive care unit was higher at 24.7%, compared to patients who were not admitted to the intensive care unit (10.5%) ($P < 0.001$). In 60.4% of patients, $P = 0.003$, the PE was peripheral. According to the authors, PE was observed in 25.3% of patients with severe COVID-19.

J. Helms *et al.* [32] and J. Poissy *et al.* [34] note that the incidence of PE is higher in patients with COVID-19 pneumonia compared to those with non-COVID-19 viral pneumonia. In the study by E. Martínez Chamorro *et al.* [33], the incidence of PE was analysed in 342 patients with severe COVID-19 and pneumonia and 147 patients with viral cases of pneumonia of other etiologies. Among patients with COVID-19, PE was diagnosed in 26% of patients, compared to 16.3% of patients without COVID-19, p=0.0197; relative risk =1.6. An increased incidence of PE is most often observed in patients with COVID-19 compared to other coronaviruses, according to W. Miesbach *et al.* [37]. The reason for this difference is the cytokine storm. According to N. Mackman *et al.* [38], SARS-CoV-2 causes similar endothelial damage.

Given the increased hepatic production of plasma fibrinogen and pulmonary epithelial fibrinogen in patients with ARDS, there have been suggestions for the use of thrombolytic therapy. The treatment of PE requires risk stratification. C. Basman *et al.* [39] write that for high-risk PE, systemic thrombolysis or embolectomy is advisable, while for low-risk PE, only anticoagulant therapy is chosen. According to P. Kapała *et al.* [35], patients with PE and normal blood pressure, but with signs of right ventricular dysfunction, form an intermediate-risk group, regarding which there are discrepancies regarding the therapeutic strategy. Approximately 10% of such patients may experience haemodynamic decompensation. Systemic thrombolysis should be considered an important treatment method, but the risks of major and intracranial bleeding compete with the overall harm from PE [40]. Numerous hybrid pharmaco-mechanical approaches have been developed to explore the advantages of thrombolysis, but the overall clinical experience with such interventional strategies is limited. Large emboli can rapidly increase pulmonary vascular resistance to a level of afterload that the RV cannot cope with. In such cases, sudden death, usually in the form of electromechanical dissociation, most often occurs. D. Barrios *et al.* [41] believe that right ventricular thrombosis increases the frequency of PE. The formation of a mobile thrombus in the right chambers of the heart, as a cause of PE, is often overlooked. A thrombus formed in the right atrial appendage is a particularly underestimated cause of PE. Right ventricular thrombi can be fixed to the heart structures. Due to the high mortality rate, such a clinical situation is a problem that requires immediate diagnosis

and treatment. Given the existing treatment options for intracardiac thrombi, the optimal therapy remains undefined, according to S. Shi *et al.* [42].

In PE not associated with COVID-19, the incidence of right ventricular thrombosis is 7-18% and is associated with a high probability of early death [30]. The primary treatment methods are thrombolysis and anticoagulants, surgical embolectomy or the use of interventional percutaneous methods, as written by M. Vlachou *et al.* [43]. The advantages of each approach vary depending on the patient's clinical condition. According to A. Anthi *et al*. [44], in the presence of an intracardiac thrombus, anticoagulant drugs can be used alone as first-line therapy. The use of anticoagulants as first-line therapy is proposed in stable patients, especially in the presence of a high bleeding risk. Even though the aforementioned drugs have not been shown to have a direct thrombolytic effect, examples of thrombus dissolution are presented in the literature. M. Vlachou *et al.* [43] believe that thrombus lysis occurs as a result of an indirect effect due to the activation of endogenous fibrinolysis.

In a study by L.M. Burgos *et al.* [45], the treatment of 207 patients with right heart chamber thrombi was analysed. PE was observed in 85% of cases. Overall mortality was 21.3%. Mortality observed after the use of anticoagulants exceeded that after surgical treatment. According to M.P. Rai *et al.* [46], there are several contraindications and limitations to anticoagulant therapy, and its effectiveness is low. The classic surgical method for solving the problem is embolectomy under cardiopulmonary bypass. Surgical treatment has several disadvantages: it is not available in all medical centres, carries the risk of delaying care for several hours, and is associated with a high level of mortality, as noted by J. Keeton *et al.* [47]. New minimally invasive methods include endovascular mechanical thrombectomy with fragmentation; and endovascular thrombus aspiration. These methods are promising, but their use is limited by availability and insufficient compelling evidence, as stated by F. Rajput *et al.* [48].

An alternative to the methods mentioned above could be thrombolysis. The advantages of using systemic thrombolysis include its availability, rapid initiation, and simplicity of the method [41]. However, thrombolytic therapy is not without risk: it can lead to the dislocation of the thrombus or its fragments and their migration to the pulmonary arteries. Although right ventricular thrombosis is considered a predictor of poor prognosis in PE, there is evidence to suggest that such thrombi are transient and should be considered as confirmation of PE. The prognosis in this case is related to haemodynamic status.

The author of the article did not find any studies describing the statistics of right ventricular thrombosis in COVID-19 patients. In the study of A. Anthi *et al*. [44] such cases are described, but without providing statistical data. Thus, at present, there are no established principles for the treatment of PE in COVID-19. Existing studies by A. Alharthy *et al.* [49] and L.C. Price *et al.* [50] described isolated successful cases of the use of thrombolytic therapy. The authors believed that thrombolysis could have a decisive therapeutic value; however, they emphasised that the risk of potential bleeding cannot be underestimated. Currently, a large randomised trial on the use of alteplase in patients with PE in the context of COVID-19, TRISTARDS [40], is underway. The study is currently in its third phase. The author of this article considers it significant that the risk of mortality increases with delays in the initiation of thrombolysis. A multifactorial analysis revealed an increase ($p = 0.034$) in the risk of death associated with deferred thrombolysis, with an OR of 1.75 (95% CI 1.04–2.93) for each day of delay (standardised for the level of PaO2/FiO2). The findings of this study suggest that thrombolysis should be administered as promptly as possible after a relevant diagnosis is established, provided that there are indications for its use. These findings align with recommendations for administering thrombolysis in patients with ischaemic stroke. Thus, the data obtained indicate a notably high prevalence of PE in patients with COVID-19 (25.3%) and a significant efficacy of thrombolysis in treating this complication.

CONCLUSIONS

The primary aim of this study was to evaluate the effectiveness of treatment for PE in the context of severe COVID-19. This objective was achieved through a meticulously designed methodology and thorough analysis of the collected data. The results indicate a high efficacy of systemic thrombolysis in the emergency treatment of patients with PE associated with severe COVID-19. The overall mortality rate in the intensive care unit was 28.6%, which aligns with global statistics. The highest risk of mortality and the need for mechanical ventilation were observed in patients classified in the fourth group. It was established that with each day of delay in administering thrombolysis, the risk of death increased ($p = 0.034$), with an OR of 1.75 (95% CI 1.04–2.93) for each additional day, even after standardisation for the level of PaO2/FiO2. Consequently, timely administration of thrombolytic therapy significantly improved treatment outcomes. A trend towards a reduction in mortality risk was also observed among patients who received thrombolysis ($p = 0.052$) compared to those who did not. These findings underscore the importance of administering thrombolytic therapy promptly in patients with PE associated with severe COVID-19 to lower mortality rates and enhance clinical outcomes. Thus, it can be concluded that systemic thrombolysis is an effective treatment method for patients with PE in the context of severe COVID-19.

This research has practical significance as it allows clinicians to reduce mortality in patients with PE in the context of severe COVID-19. Factors such as the patient's respiratory status, the timeliness of prescribing thrombolytic therapy, and the state of the coagulation system should be carefully analysed. Decisions on the prescription of thrombolytic therapy should be made as soon as possible. Limitations of the study were attributed to the small number of patients examined and its single-centre design. Future studies on the effectiveness of thrombolytic therapy in the context of COVID-19 and PE, if conducted, may provide a greater understanding of the pathogenetic factors of the disease and the mechanisms of action of the therapy used.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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Ефективність тромболітичної терапії у хворих на COVID-19 важкого перебігу та тромбоемболію легеневої артерії

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Анотація. Дані сучасних досліджень містять недостатньо інформації про використання тромболітичної терапії у лікуванні тромбоемболії легеневої артерії на тлі COVID-19. Наявні дослідження містять дані про ефективність терапії тромболітичними препаратами тромботичних ускладнень COVID-19, важкого перебігу. Проте наявні роботи або стосуються зовсім малої кількості спостережень, або залишаються не закінченими. Метою даної статті було оцінити ефективність системного тромболізису у вигляді довенного введення альтеплази при цій патології. Було проаналізовано дані медичних карт 92 пацієнтів. Пацієнтів ділили на чотири групи в залежності від проведеної терапії. Пацієнти першої групи, мали ускладнення у вигляді промбоемболії легеневої артерії, проте не потребували застосування тромболітичної терапії. Лікування пацієнтів першої групи полягало у призначенні низькомолекулярного гепарину в лікувальній дозі. Пацієнти другої та третьої груп на тлі COVID-19 мали тромбоемболію легеневої артерії та потребували тромболітичної терапії. Відмінністю третьої групи від другої була наявність тромбу у правій половині серця. Пацієнти четвертої групи мали ускладнення у вигляді тромбоемболії легеневої артерії, потребували тромболітичної терапії, проте не отримували останню в зв'язку з відсутністю коштів на лікування. Лікування пацієнтів другої та третьої груп полягало в негайній терапії нефракціонованим гепарином та альтеплазою. В четвертій групі тромболізис не проводився. Було досліджено смертність пацієнтів в залежності від встановленої групи. Було встановлено, що ризик летального випадку збільшувався ($p < 0,001$) при зростанні рівня Д-дімеру та зменшувався при зростанні PaO2/FiO2 ($p < 0,001$). За наявності тромбу у правих відділах серця ризик летального випадку зростав ($p = 0,002$), ВШ = 3,97 (95 % ВІ 1,66–9,49). Виявлено тенденцію до зниження ризику летального випадку при проведенні тромболітичної терапії ($p = 0,052$). Було узагальнено дані щодо зростання ($p = 0,009$) ризику летального випадку при відтермінуванні тромболізісу. Смертність пацієнтів четвертої групи становила 100 %. Отримані дані свідчать про про значну ефективність тромболітичної терапії у лікуванні даної патології

Ключові слова: тромболізис; гострий респіраторний дистрес синдром; альтеплаза; нефракціонований гепарин

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Functional-structural reorganisation of salivary glands in oncological pathology: A mini-review

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Abstract. Dysfunctions of salivary glands during the treatment of benign and malignant tumours are a widely diagnosed problem among oncology patients. This study aimed to investigate the disruption of the structure of salivary glands as a result of the treatment of oncological diseases and methods for their correction and elimination. 39 scientific papers were analysed. Methods of search, comparison, systematisation, and combination of the results of the conducted studies were used. The destructive effect of chemo- and radiotherapy and the treatment of malignant tumours by increasing the body's overall temperature on the structure of salivary glands in the experiment was proven. The influence of low-intensity ultrasound on the submandibular gland demonstrates its tissues' high adaptive and regenerative properties. Data from clinical studies on the correction and elimination of salivary gland dysfunctions in oncological patients showed an ambiguous result. The simultaneous application of photobiomodulation and radiotherapy in patients with head and neck tumours significantly improves organ function: it stimulates salivation, regulates saliva composition, controls the redox mechanism of salivary glands, and locally eliminates inflammation. A slight compensation of the mineralising function of saliva was found with substitution therapy using biologically active components and a remineralising agent in children with malignant tumours undergoing chemotherapy. A positive effect of betanechol and vitamin E in protecting salivary glands during the treatment of head and neck cancer with radiotherapy has been noted, which consists of improving the structure and function of the glands in the long term and is the same in women and men. Studies of vitamin C intake after radioiodine therapy in patients with head and neck cancer have shown its insufficient restorative effect on the quantitative and qualitative composition of saliva. The results of this review can serve as a basis for an accurate assessment by oncologists of salivary gland damage and the pathogenesis of their dysfunctions as a result of cancer therapy, provide an opportunity to reconsider existing views on the problem, develop new methods for preventing and treating these complications, and improve the quality of life and recovery process for patients

Keywords: oncology; dysfunction; chemotherapy; morphometry; radiation

INTRODUCTION

At the present stage of human evolution, cancer incidence worldwide continues to rise steadily year by year, with GLOBOCAN 2020 projecting a 47% increase in diagnosed cancer cases over the next 20 years [1]. In treating cancer patients, clinicians employ advanced surgical techniques, precise and safe radiotherapy, polychemotherapy, and hormone therapy, as well as innovative methods such as interventional radiology, immunotherapy, and targeted therapy. However, these treatments often lead to the development of so-called drug-induced iatrogenic conditions, disrupting the functioning of the patient's organs and systems, as described by S.M. Schleicher *et al.* [2]. The onset of concurrent dental pathology is no exception among oncology patients. J.Y.A. Kyaw *et al.* [3] highlight the link between systemic cancer treatment and salivary gland damage, leading to dysfunctions such as hyposalivation and xerostomia, which are the most common. Saliva plays a crucial role in maintaining homeostasis, preserving the integrity of oral tissues, and supporting the natural digestive processes. Therefore, ensuring the proper functioning

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of saliva is particularly important in conditions that impair salivary gland activity, as pointed out in the study by N. Gevkaliuk *et al.* [4].

The onset of xerostomia, commonly known as "dry mouth", is a frequent complication of cancer treatment. Patients often experience thirst, difficulties in eating, altered taste perception, speech impairments, roughness of the oral mucosa, as well as periodic pain and burning sensations in the mouth, all of which significantly reduce their quality of life. T.S. Deshpande *et al.* [5] found a strong positive correlation between xerostomia and dysgeusia in both the short- and long-term among patients with oropharyngeal cancer who underwent proton therapy. The examinations were conducted at 2 weeks, 8 weeks, 6 months, and 2 years post-treatment, with xerostomia and dysgeusia being present at all time points. In a literature review, L.T. Galaniha & A.A. Nolden [6] identified taste dysfunction in 17.6-93% of cancer patients and xerostomia in 40.4-93% as two of the most common symptoms during cancer and its treatment. Y. Iijima *et al.* [7] observed grade 1 dysgeusia (altered taste sensation) and hyposalivation caused by chemotherapy in patients with colorectal, breast, and gynaecological cancers. I.M.V. Silva *et al.* [8] demonstrated in a clinical study of breast cancer patients that quality of life deteriorated after just the second cycle of antitumour therapy. They attributed the altered taste and xerostomia to the cytotoxic effects of chemotherapy, leading to loss of appetite, early satiety, nausea, and reduced overall food intake, which in turn has psychological and social consequences for the patient. I. Brook [9] identified long-term side effects in patients undergoing radiotherapy for head and neck cancer, highlighting hyposalivation and xerostomia as prominent issues. To treat salivary gland dysfunction, the author suggests the use of saliva substitutes, non-pharmacological saliva stimulation, salivary stimulants, laser treatment, and increased fluid intake. R.R. Riantiningtyas *et al.* [10] conducted a cross-sectional study in head and neck cancer patients using psychophysical tests to assess tactile sensitivity, the ability to discern food texture and temperature, as well as salivary function, consistency, pH, volume, and buffering capacity. They found a low somatosensory response in these patients, which was linked to reduced salivary secretion. Z. Huang *et al.* [11] investigated the prevalence of salivary gland damage caused by radioactive iodine, assessing progressive changes in the glands through ultrasound imaging. In patients who underwent total or near-total thyroidectomy followed by postoperative radioiodine therapy, ultrasound-detected salivary gland alterations increased from 2.0% to 33.0% after 20 months, with most of these changes persisting at 36 months, indicating irreversible gland damage. A literature review by B.A. Klein *et al.* [12] demonstrated that immune system-related side effects are common and can affect any organ system, including exerting toxic effects on the salivary glands.

Despite significant advancements in cancer treatment, chemotherapy, radiotherapy, and radiation therapy remain the primary methods for cancer treatment, yet they cause a range of side effects. The most common among these are xerostomia and altered taste, which contribute to loss of appetite, cachexia, and reduced resistance in patients already weakened by their primary disease – the tumour. Physicians and scientists worldwide are investigating these issues to alleviate the suffering of cancer patients and improve their quality of life and recovery process. This study aimed to analyse the structural changes in salivary glands during cancer treatment and explore methods for preventing and mitigating these effects.

To achieve the stated objective, a comprehensive literature search was conducted on the PubMed, Medline, and Scopus platforms. Over 50 publications, including clinical data, experimental studies, and literature reviews, were analysed. The search strategy was developed following the PICOS framework. A systematic search was performed using relevant keywords and search terms aligned with the PICO criteria. The study investigated the impact of the most common cancer therapies across different tumour locations, their side effects – particularly the damage to the structure and function of the salivary glands – and measures aimed at improving or restoring the function of these organs. The inclusion criteria for publications were the originality of data, clinical and experimental results published in Ukrainian, English, and Russian (as a significant number of professional publications in Ukraine were published in Russian before 2014). Studies that lacked control group data in clinical trials, as well as those only available as conference abstracts or in collections of scientific papers, as well as research abstracts, were excluded from this review. During the search for verification methods of salivary gland damage, prevention, and treatment in cancer therapy, a shortage of literature from 2018 onwards was identified, prompting an extension of the review period to cover 2006 to 2023. As a result, 39 sources were included in this study.

MORPHOMETRY OF SALIVARY GLANDS UNDER VARIOUS CANCER TREATMENTS IN EXPERIMENTAL STUDIES

Chemotherapy is widely used in oncology treatment. S. Herashchenko *et al.* [13] analysed and described changes in the submandibular salivary gland under the influence of cisplatin, demonstrating that intraperitoneal administration of cisplatin to rats over 9 weeks resulted in both degenerative and compensatory changes in the parenchyma and stroma of the gland, including fibrosis of the interductal connective tissue. Throughout the experiment, the acini appeared collapsed, with a reduction in their external diameter and area compared to controls, along with a decrease in the height and number of serous cells. The intercalated ducts exhibited varying changes in external diameter and lumen size, showing both decreases and increases (the highest values observed on day 28). In striated ducts, the external diameter progressively increased, while the lumen decreased. The interlobular ducts consistently showed an increase in both external diameter and lumen size. From day 3 to day 28, the epithelial cells of the intercalated, striated, and interlobular ducts showed signs of sloughing, with their number and height decreasing up until day 14, after which regeneration began. In the periductal stroma, fibrosis increased up to day 28, with activated fibroblasts (showing large connective tissue bundles) being observed, as reported by R.A.L. Willems e*t al.* [14], C.C. Kirwan & E.L. Blower [15]. A. Farokh e*t al.* [16], and S.R. Bomeli Farokh e*t al.* [17] investigated the effects of radiation on the submandibular glands of rats 180 days post-irradiation. They found that during this period, diffuse fibrosis

developed in both the inter- and intralobular stroma, indicating long-term structural changes and damage resulting from radiation exposure.

L. Radfar & D.A. Sirois [18] developed a model of radiation-induced salivary gland injury in Hanford minipigs using the same irradiation protocol employed in contemporary clinical practice, which involved a daily radiation dose of 70 Gy. The irradiated glands exhibited significant loss of parenchyma, pronounced atrophy, and interstitial fibrosis of the acinar cells, along with an increase in the nuclei of these cells, as well as dilation and proliferation of the excretory ducts. This was accompanied by a loss of secretory granules and infiltration of lymphocytes and plasma cells. Notably, these structural changes were more pronounced in the submandibular glands compared to the parotid glands, as noted by F. Huisman *et al.* [19] and V. Mercadante *et al.* [20]. E. Bidram *et al.* [21] discovered that the lumens of the excretory ducts of the submandibular glands contained sloughed epithelial cell layers.

Ultrasound is frequently employed to stimulate and accelerate physiological reactions or to selectively disrupt tissues in the jaw through heating methods or by enhancing the plasticity of bone tissue, as indicated by B de Lucas *et al.* [22]. L. Tarasenko & M. Bilets [23], along with V.N. Patel & M.P. Hoffman [24], investigated the stress factor associated with the effects of low-intensity ultrasound on the submandibular gland. The following results were interpreted: dilation of the excretory ducts with flattened, vacuolated epithelial cells, a significant predominance of mucous secretion over protein secretion, accumulation of lymphocytic cells and macrophages around microvessels while preserving structural components, and an increase in the number of mast cells in the interlobular connective tissue and the stroma of the interlobular vessels at the beginning of the experiment, with subsequent subsidence of these processes in the later stages. Chemotherapy, radiation exposure, and hyperthermia in experimental animals lead to the destruction of salivary gland structures. Ultrasonic correction of bone tissue has an impact on the structure of the submandibular salivary gland, suggesting high adaptive and regenerative properties of its tissues.

METHODS OF CORRECTION AND ELIMINATION OF SALIVARY GLAND DYSFUNCTIONS

In a clinical study by G.C. Louzeiro *et al.* [25], the impact of photobiomodulation on salivary secretion, saliva composition, xerostomia, and the quality of life of patients undergoing radiotherapy for head and neck cancers was evaluated over a short-term observation period. A diode laser was employed for intraoral and extraoral applications to the salivary glands, administered three times a week throughout the radiotherapy course. Xerostomia and salivary pH were assessed, and both unstimulated and stimulated salivary secretion were measured before the onset of radiotherapy, after the 15th session, upon completion of radiotherapy, and 60 days post-treatment. The concentrations of calcium, total proteins, chloride, sodium, potassium, and the activity of amylase and catalase were evaluated in stimulated saliva samples. Researchers T.D. Debela *et al*. [26] and P. Roth *et al.* [27] demonstrate that photobiomodulation can stimulate salivary secretion, regulate the composition of saliva, and control the redox mechanisms of salivary glands, thereby reducing local inflammation when applied concurrently with radiotherapy. However, the question remains as to whether the increase in salivary secretion can be sustained, whether it has a radioprotective effect and whether it can be widely applied in clinical settings.

P. Tkachenko *et al.* [28] conducted a study on the salivation rate and mineralising potential of oral fluid, along with their correction in children with malignant soft tissue tumours of various anatomical locations. The study involved a group of children aged 7 to 15 with morphologically verified soft tissue malignancies that were responsive to chemotherapy (such as nephroblastoma, hepatoblastoma, rhabdomyosarcoma, retinoblastoma, reticulosarcoma, and central nervous system tumours). The patients underwent courses of combined chemotherapy lasting 3-4 weeks. The first group of children was treated according to the standard medical care protocol for this category of patients, with the addition of a conventional oral care regimen. In the second group of study participants, in addition to the standard treatment, gel-based preparations were administered as part of a replacement therapy. These gels contain biologically active components (centaury, echinacea, sage), which stimulate the functional activity of the salivary glands, possess anti-inflammatory properties, and a remineralising gel with calcium, fluoride, and phosphorus. The research was conducted before the commencement of treatment and following the completion of the first course of polychemotherapy. In the first group of children, there was a progressive decrease in the mineralising potential of the oral fluid during the polychemotherapy, accompanied by a reduction in salivation rate. In the second group, only partial compensation of this mineralising imbalance was observed, as reported by .A. Nolden *et al*. [29] and A.K. Larsen *et al*. [30].

A significant portion of the research by S. Manoharan *et al*. [31] and S. Campagna *et al*. [32] is focused on finding methods to protect and prevent damage to the salivary glands during radiotherapy for head and neck cancers. D. Campanhã *et al*. [33] proposed the use of bethanechol to prevent salivary gland dysfunction in patients undergoing radioactive iodine therapy. Patients received bethanechol (25 mg twice daily) or a placebo (control group) two hours after therapy and for up to one month. Saliva flow was monitored, and quality of life was assessed using the University of Washington Quality of Life Questionnaire at 10-, 30-, and 90-day post-therapy. Pain and swelling of the salivary glands were more common among patients taking the placebo at both 10 and 30 days. Those in the bethanechol group demonstrated improved saliva production and a more positive outlook. Bethanechol proved effective in reducing acute salivary gland damage.

A. Upadhyaya *et al*. [34] studied the radioprotective effect of vitamin E on the parotid and submandibular salivary glands following radioiodine therapy for differentiated thyroid cancer. Patients in the three study groups received vitamin E orally at doses of 100, 200, and 300 mg/day for 1-4 weeks after therapy. Salivary gland function was assessed using salivary gland scintigraphy immediately before and six months after treatment. The findings of T. Buttiron Webber *et al*. [35] and L.T. Tchelebi *et al*. [36] demonstrated improved functional parameters of the salivary glands,

indicating a high compensatory capacity of the major salivary glands, with vitamin E showing significant protective effects on both parotid and submandibular glands in both men and women.

Y. Liu *et al.* [37] conducted a study on the protective effects of vitamin C on salivary glands following iodine-131 therapy in patients with differentiated thyroid cancer. To determine the optimal timing of vitamin C administration, patients were divided into two groups: a 2-hour group and a 24-hour group based on the time of vitamin intake post-radiation therapy. They received 100 mg of vitamin C every hour (excluding sleep from 23:00 to 6:00) for five consecutive days. Clinical symptoms such as swelling, pain, dry or bitter mouth, dysphagia, reduced taste, and the function of major salivary glands were evaluated, including secretion index and saliva concentration index. The study found that I^{131} treatment caused some salivary gland damage: the incidence of gland injury (17.39%) in the 2-hour group was lower compared to the 24-hour group (26.96%). The frequency of acute gland injury (15.22%) and chronic gland injury (26.09%) in the 24-hour group was higher than in the 2-hour group (4.78% and 18.26%, respectively). Differences in the concentration indices of the left and right submandibular glands were observed after treatment in both groups, indicating a limited protective effect of vitamin C administration post-I^{131} therapy, as noted by G. Hayek & B. Kastler [38] and M. Faruque *et al*. [39].

Photobiomodulation can stimulate saliva production, regulate its composition, and control the redox mechanism of the salivary glands, reducing local inflammatory processes when used alongside radiation therapy. However, its long-term application requires further investigation. Replacement therapy with biologically active components that stimulate the functional activity of the salivary glands, combined with anti-inflammatory agents and remineralising treatments during polychemotherapy, provides only partial compensation for the remineralising function of saliva and does not affect its secretion rate. Oral administration of the parasympathomimetic bethanechol and vitamin E protects the salivary glands from damage during radiotherapy and enhances salivation. Vitamin C, used as a protector of the salivary glands during iodine-131 therapy, did not achieve the desired effect.

CONCLUSIONS

The salivary glands are highly sensitive organs in various approaches to cancer treatment and often respond with partial or complete loss of function, leading to a significant decline in dental health, well-being, and overall quality of life for patients during therapy.

Studies on the effects of various cancer treatments on the submandibular salivary gland in experimental animals have revealed several morphological changes. Chemotherapy induces both degenerative and compensatory changes in the gland's parenchyma and stroma, accompanied by fibrosis of the interductal connective tissue. Radiation exposure leads to the destruction of epithelial cells in the granular excretory ducts and terminal sections, followed by short-term regenerative responses. However, after prolonged periods post-irradiation (180 days), there are disruptions in the nuclear-cytoplasmic ratios of exocrine cells, a reduction in interstitial space, and the accumulation of secretions in serous cells. High-frequency heating causes venous hyperaemia, stasis, hypertrophy, an increase in capillary numbers, and excessive detachment of epithelial cells in the excretory ducts. The use of ultrasound for selective tissue destruction of jaw tissues, activation of degenerative changes in glandular cellular structures at the beginning of the experiment and restoration of their structure and function in the long term are observed.

The use of photobiomodulation alongside radiotherapy has demonstrated positive outcomes in stimulating salivation, regulating saliva composition, and maintaining the redox mechanism in salivary glands, while also reducing inflammation. Topical applications of gel-based treatments containing functional salivary gland stimulants, anti-inflammatory agents, and remineralising properties, when administered during chemotherapy, proved insufficiently effective and resulted in only partial compensation of mineral imbalance. Betanechol, used as a radioprotective agent, effectively reduced acute salivary gland damage, improving both physiological and subjective health indicators in patients. A six-month follow-up of patients who received vitamin E after iodine-131 therapy for thyroid cancer showed an improvement in the functional performance of major salivary glands, confirming the substantial restorative effect of this vitamin on the glands in both men and women. Short-term vitamin C intake following radioiodine therapy produced only a minor positive effect.

The onset and progression of structural and functional reorganisation of the salivary glands in oncological pathology necessitate exploring unconventional perspectives on the issue, as well as the development of innovative methods and approaches for its prevention, the restoration of glandular structure and function, and subsequent rehabilitation measures for clinical application. Greater emphasis should be placed on the use of supplementary diagnostic techniques for assessing salivary gland damage, including morphometric analysis, which enables the identification of specific structural changes and supports a more individualised approach to selecting corrective treatment methods.

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CONFLICT OF INTEREST

None.

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Структурно-функціональна реорганізація слинних залоз при онкопатології: міні огляд

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Анотація. Дисфункції слинних залоз при терапії доброякісних та злоякісних пухлинних захворювань є широко діагностованою проблемою серед онкопацієнтів. Метою даної роботи стало вивчення порушення структури слинних залоз внаслідок лікування онкологічних хвороб та методів їх корекції й усунення. Було проаналізовано 39 наукових робіт. Використано методи пошуку, порівняння, систематиції та об'єднання результатів проведених досліджень. Доведено деструктивний вплив хіміо-та радіотерапії, лікування злоякісних пухлин шляхом підвищення температури всього тіла на структуру слинних залоз в екперименті. Вплив ультразвуку низької інтенсивності на піднижньощелепну залозу демонструє високі адаптивні та регенеративні властивості її тканин. Дані клінічних досліджень щодо корекції та усунення дисфункцій слинних залоз у окохворих показали неоднозначий результат. Застосування фотобіомодуляції одночасно із променевою терапією у пацієнтів із пухлинами голови чи шиї значно покращує функціонування органа: стимулює слиновиділення, регулює склад слини, контролює окислювально-відновний механізм слинних залоз та місцево усуває запалення. Виявлено незначну компенсацію мінералізуючої функції слини при замісній терапії біологічно активними компоненнтами та ремінералізуючим препаратом у дітей зі злоякісними пухлинами при хіміотерапії. Відмічається позитивний ефект застосування бетанехолу та вітаміну Е у протекції слинних залоз при лікуванні раку в ділянках голови та шиї методом радіотерапії, який полягає у покращенні стуктури та функції залоз у довготривлому періоді та є однаковим у жінок і чоловіків. Дослідження вживання вітміну С після радіойодтерапії у пацієнтів з раком голови чи шиї показало його недостатній відновлюваний ефект кількісного і якісного складу слини. Результати проведеного огляду можуть стати підгрунтям для точної оцінки онкологами уражень слинних залоз та патогенезу їх дисфункцій внаслідок онкотерапії, надати можливість переглянути вже існуючі погляди на проблему, розробити нові методики запобігання і лікування вказаних ускладень, покращити якість життя і процес видужання пацієнта

Ключові слова: онкологія; дисфункція; хіміотерапія; морфометрія; радіація

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