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DYNAMICS OF THE LEVEL OF INFLAMMATION MARKERS IN PATIENTS WITH FRACTURES OF LONG BONES AGAINST THE BACKGROUND OF COVID-19

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The purpose of the study was to determine the response dynamics of inflammatory markers C-reactive protein and procalcitonin in patients with long bone fractures against the background of COVID-19. The main group included 157 cases of skeletal fractures against the background of COVID-19, and the control group included 132 cases of skeletal fractures in which there was no COVID-19 infection. The dynamics of the C-reactive protein level in patients with fractures against the background of COVID-19 indicated that this inflammatory marker is not informative at the initial stage, however, starting from the 3rd day, a significant increase in the C-reactive protein level was noted with a subsequent drop in the level in the postoperative period on the 10th day of treatment. The dynamics of the procalcitonin level was approximately the same during all observation periods and did not reflect the changes that occurred in patients with long bone fractures against the background of COVID-19, which does not allow the use of this inflammatory marker in the clinical diagnosis of the course of COVID-19 in patients with long bone fractures

Key words: trauma, COVID-19, C-reactive protein, procalcitonin

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ДИНАМІКА РІВНЯ МАРКЕРІВ ЗАПАЛЕННЯ У ХВОРИХ З ПЕРЕЛОМАМИ ДОВГИХ КІСТОК НА ТЛІ COVID-19

Метою дослідження було визначити динаміку відповіді маркерів запалення С-реактивний білок та прокальцитонін у пацієнтів з переломами довгих кісток на тлі COVID-19. До основної групи були віднесені 157 випадки переломів скелета на тлі COVID-19, у контрольну групу увійшло 132 випадки переломів скелета, в яких була відсутня COVID-19 інфекція. Динаміка рівня С-реактивний білку у пацієнтів з переломами на тлі COVID-19 вказала, що на початковому етапі цей маркер запалення не є інформативним, однак починаючи з 3 дня відмічалось значне підвищення рівня С-реактивний білок з послідовним падінням рівня у післяопераційному періоді на 10 добу лікування. Динаміка рівня прокальцитоніну була приблизно однаковою в усі терміни спостереження і не відображала зміни, що відбувались у пацієнтів з переломами довгих кісток на тлі COVID-19, що не дозволяє використовувати даний маркер запалення у клінічній діагностиці протікання COVID-19 у пацієнтів з переломами довгих кісток

Ключові слова: травма, COVID-19, С-реактивний білок, прокальцитонін

The study is a fragment of the research project "Fractures of long bones in patients with COVID-19 (diagnosis, clinical features and the course of the traumatic process)", state registration No. 0123U103221.

In the first months of the COVID-19 pandemic, humanity faced the problem of high-quality and accurate diagnosis of the virus in patients. Not all known methods of diagnosing viral diseases were adequate in the early diagnosis of COVID-19. Knowledge of diagnostic tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still evolving, and a clear understanding of the nature of the tests and the interpretation of their results is important.

Today, it is clear that the COVID-19 pandemic has become a challenge for the healthcare system in all countries. Vast financial and human resources are involved in providing care to infected patients. Many multidisciplinary hospitals have been repurposed into infectious diseases hospitals. In the conditions when the pandemic is in full swing, it is also necessary to solve the issue of specialized trauma care [1].

C-reactive protein (CRP) is among the most widely used inflammation markers actively used in modern orthopedics and traumatology. Today, this marker of inflammation is one of the most informative in the diagnosis of infectious complications among patients with polytrauma [7]. However, is it possible to use it in the early diagnosis of complications in patients with COVID-19? Is it informative in different periods of traumatic illness against the background of COVID-19? It is common knowledge that CRP belongs to the early markers of inflammation and can give a reaction already on the first day of the disease, however, we did not find data indicating its response to the combined effect of trauma and the COVID-19 virus in the available literature

One rather sensitive laboratory marker for early diagnosis of the occurrence and development of infectious complications in patients with fractures was the blood procalcitonin test. Procalcitonin (PCT) was first described in 1984 as a protein consisting of 116 amino acids and a molecular weight of 14.5 kDa. In the beginning, PCT was taken into account as a possible marker of the oncological process. However, later it was found that the increase in the level of PCT in patients with infection is significantly higher than in patients with neoplasms. Since 1992, this test has gained more and more popularity in the world in the early diagnosis of surgical infection. The concentration of PCT in the blood is very low and is at the level of 0.1–0.5 ng/ml in healthy donors. It is known that high titers of the procalcitonin level indicate the development of a severe infection, which is especially important in patients who have fractured long bones and are sick with COVID-19 [11].

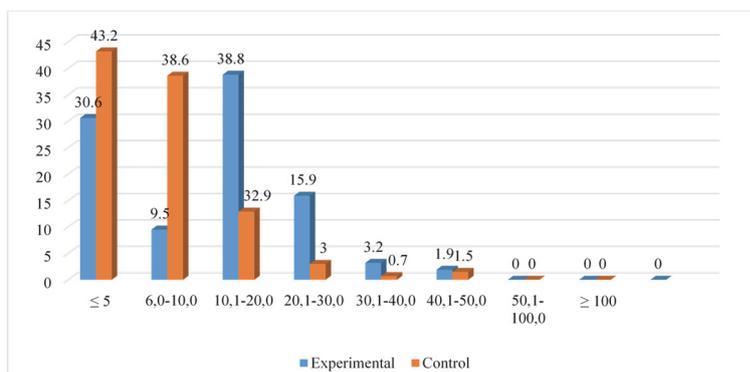
In the available literature, there are several reports on the response of inflammatory markers in the early diagnosis of complications of COVID-19 in long bone fractures, but studies on the dynamics of their levels have not been found. Considering the above, we considered it necessary and expedient to conduct this research.

The purpose of the study was to determine the response dynamics of inflammatory markers C-reactive protein and procalcitonin in patients with long bone fractures against the background of COVID-19.

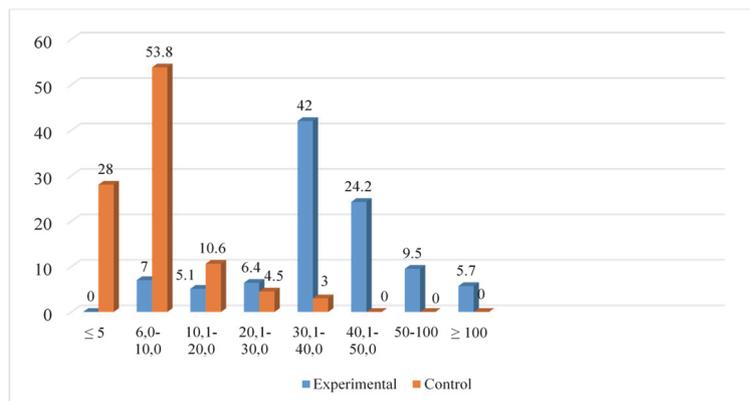
Materials and methods. To fulfill the tasks of the study, we formed a retrospective array of the study, which consisted of 289 cases of fractures of the bones of the skeleton, which were treated in the KNP “Kyiv City Clinical Hospital of Emergency Medical Care” from March 2020 to February 2021 and met the criteria for inclusion in the study. The total array of the study was 289 cases of fractures of the bones of the skeleton, which were divided into two groups: the main and the control. 157 cases of skeletal fractures against the background of COVID-19 were included in the main group and met the selection criteria for the study. In relative terms, this accounted for 54.3 % of the total array. The control group included 132 cases of skeletal fractures in which there was no COVID-19 infection and also met the selection criteria for the control group. In relative terms, this accounted for 45.7 % of the total array. In the main group, there were 88 men, which constituted 56.0 % of the mass of the group, and 69 women, respectively, which constituted 44.0 % of the mass of the group. The average age in the group was 52.1 ± 8.8 years. In the control group, there were 82 men, which constituted 62.1 % of the mass of the group, and 50 women, which constituted 37.9 % of the mass of the group. In order to qualitatively diagnose the reaction of inflammatory markers in patients with long bone fractures against the background of COVID-19, we conducted his study on the first, third and tenth day of treatment. Statistical processing was carried out using non-parametric methods. Taking into account the number of analyzed signs and the need to ensure the uniformity of the effective indicators, in order to make a correct comparison, we chose the method of calculating the coefficient of the polychoric relationship indicator proposed by K. Pearson.

Results of the study and their discussion. It is common knowledge that CRP is one of the early markers of inflammation and can give a reaction already on the first day of the disease, however, we did not find data indicating its response to the combined effect of trauma and the COVID-19 virus in the available literature. There is no reference value for CRP, but an indicator of up to 5 mg/l is permissible. Taking into account the above, we conducted an integral analysis of the level of CRP in the patients of the study group. Taking into account the diverse clinical course of the COVID-19 infection in patients with long bone fractures, we conducted a study of CRP on the 1st, 3rd, and 10th day of treatment, which was in accordance with the recommendations of “Clinical management of patients with COVID-19. Live clinical instruction”. Fig. 1A shows the levels of C-reactive protein in patients of observation groups on the first day of treatment.

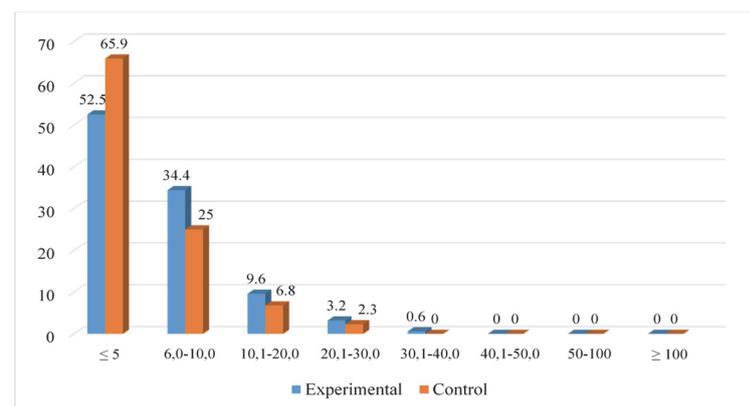
Thus, the analysis of the distribution of the CRP level in the patients of the study array on the first day indicated that among patients with fractures against the background of COVID-19, elevated CRP levels of 10–30 mg/l prevailed, which was found in 54.7 % of patients, which is three times more often than in the control group. Normal and subnormal levels of CRP were detected in 40.1 % of cases, but this is twice as rare as in patients of the control array. High levels of CRP in the main array occurred only in 5.1 % of cases, but in the control array, this level occurred twice as often. Ultra-high levels of CRP were not detected in both massifs. The conducted polychoric analysis indicated an existing positive, pronounced relationship, and the indicated positions are within the probability field ($\chi^2 43.35 \geq \chi^2_{st} 14.1$) ($p \leq 0.05$).



A



B



C

Fig. 1 Levels of C-reactive protein in patients of observation groups (A – on the first day of treatment), (B – on the third day of treatment), (C – on the tenth day of treatment).

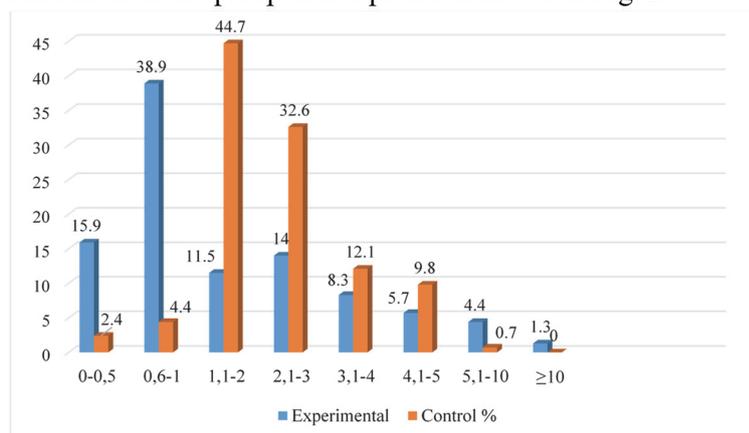
The analysis of the CRP level in the preoperative period indicated that 93.0 % of patients in the main group had a clinically significant increase in CRP: 11.5 % had moderate increase, 66.2 % – a significant increase, in 15.2 % – a high level. In the main group, CRP was most often detected at the level of 30–40 mg/l. Fig. 1B Levels of C-reactive protein in patients of observation groups on the third day of treatment. This level of CRP was present in 42.0 % of patients in the main group. Extremely high levels of CRP 50–100 mg/l among patients of the main group were found in 9.5 % of cases. Critically high levels of CRP ≥ 100 mg/ml were found in 9 patients of the main group, which was 5.7 % of the group. It is worth noting that the highest CRP level was 169 mg/l in a 74-year-old patient with a fracture of the proximal femur with concomitant pneumonia and type II diabetes. Among patients in the control group, 81.8 % had a normal or subnormal level of CRP, and only 18.1 % of patients had a clinically significant increase in CRP up to a maximum of 40 mg/l. The calculated probability indicators indicated that there is a positive, pronounced relationship between the indicated signs, and the indicated positions are within the probability field ($\chi^2 14.45 \geq \chi^2_{st} 14.1$) ($p \leq 0.05$).

CRP levels in patients of observation groups on the 10th day of treatment in the postoperative period are shown in Figure 1C. Analysis of the CRP level on the 10th day of treatment revealed peculiarities of distribution in the study array. Thus, among the patients of the main group, 52.2 % of patients had a decrease in the level of CRP to a normal level of 0–5 mg/l. The majority of patients with a normal CRP level were observed in the control group. Among patients of the control group, a normal level of CRP was found in 65.9 % of cases. The general trend among the patients of the main array was the normalization of the CRP level. Only 13.4 % of patients in the main group had an elevated level of CRP, but only 0.6 % of patients in this group on day 10 had an increase in the level of CRP to 30–40 mg/ml. The indicator of 33.8 mg/l was found in 1 patient with an infectious complication in the area of surgical intervention after osteosynthesis of the distal part of the tibia.

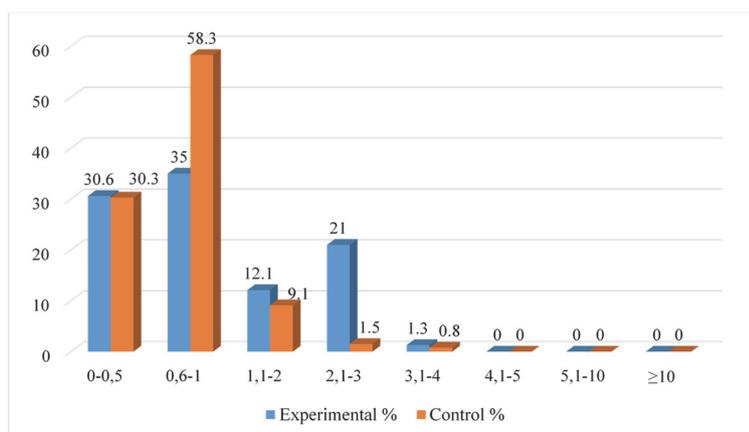
The results of the PCT level on the 1st day of treatment in the study array are shown in Figure 2A. The analysis of the PCT level in patients with long bone fractures against the background of COVID-19 indicated the following features of distribution. More than half of the patients in the main array had normal and subnormal PCT levels, but in the control array, there were 1.4 times more such patients.

An increase in the level of PCT to the average values was observed in approximately the same percentage of cases (25.5 % in the experimental group and 21.9 % in the control group). A high level of PCT up to 5 ng/ml was observed in 14.0 % of the main group, while it was only 0.7 % in the control group of patients.

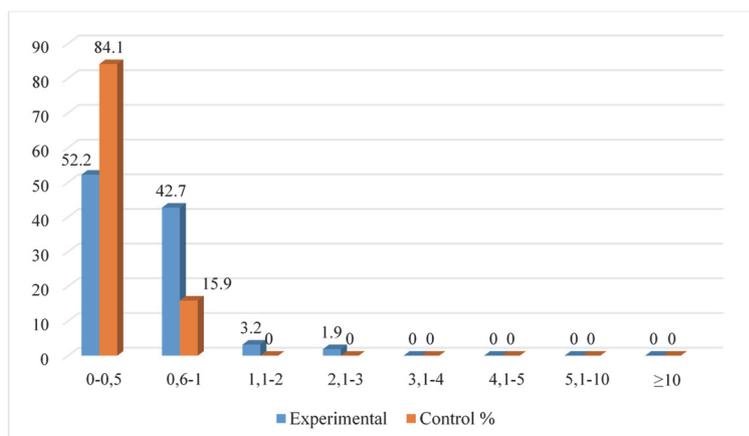
The distribution of the CRP level in the patients of the array of observation groups on the 3rd day of treatment in the preoperative period is shown in Fig. 2.



A



B



C

Fig. 2 Procalcitonin levels in patients of observation groups (A – on the first day of treatment), (B – on the third day of treatment), (C – on the tenth day of treatment).

The distribution of the PCT level on the tenth day of treatment is shown in Figure 2C. The analysis of the PCT level on the tenth day of treatment of patients with long bone fractures against the background of COVID-19 indicated that in 94.9 % of patients in the main group, the PCT level was found to be at a normal or subnormal level, which relative to the PCT level in the control group, where such indicators were registered in 100.0 % of cases. A moderate increase in PCT was observed in 5.1 % of patients in the main group, and an increase above 3 ng/ml was not detected.

Most patients with COVID-19 have a mild flu-like illness or may be asymptomatic. A small proportion of patients develop severe pneumonia, acute respiratory distress syndrome, multiple organ failure, and may even die. Why some people become critically ill and others do not remain an unsolved mystery. Comorbidities and laboratory markers have been proposed for risk stratification [8]. There is increasing evidence that critically ill patients exhibit signs of hyperinflammation, including elevated C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and hyperferritinemia. These results suggest a possibly crucial role of the cytokine storm in the pathophysiology of COVID-19 [11] In the systemic phase

Among the patients of the experimental group, 5.7 % of the patients had an extremely high level of PCT, and among the patients of the control group, such patients were not found. The calculated probability indicators indicated that there is a positive, pronounced relationship between the indicated signs, and the indicated positions are within the probability field ($\chi^2 31.79 \geq \chi^2_{st} 14.1$) ($p \leq 0.05$).

Analysis of the PCT level in patients of the experimental and control groups on the 3rd day of treatment is shown in Figure 2B.

Patients with a subnormal PCT level in the main group were found in 35.0 % of cases. It was these patients who ranked first in the main group. Among patients in the control group, a subnormal PCT level was detected in 58.3 % of cases, which is 1.7 times more. Two-thirds of patients in the experimental group had a normal or subnormal PCT level, but this is 1.3 times less than in the control group. A moderate increase in PCT was found in almost a third of patients in the experimental group, but it was almost three times more than in the control group. High levels of PCT were not detected in both experimental groups. The calculated probability indicators established that there is a positive, strong relationship between the specified signs, and the specified positions are within the probability field ($\chi^2 72.25 \geq \chi^2_{st} 14.1$) ($p \leq 0.05$).

of hyperinflammation of COVID-19, proposed by Siddiqi and Mehra (2020), there is a significant increase in inflammatory cytokines and biomarkers such as interleukin (IL)-2, IL-6, IL-7, granulocyte colony-stimulating factor, macrophage inflammatory protein 1- α , tumor necrosis factor- α (TNF- α), CRP, ferritin, PCT, and D-dimer. This stage consists of the most severe manifestation of the cytokine storm, in which excessive hyperinflammation can lead to cardiopulmonary collapse and multiple organ failure. CRP is an acute-phase inflammatory protein produced by the liver that can be elevated in several conditions, such as inflammation, cardiovascular disease, and infection [10]. In our study, elevated CRP was associated with severe COVID-19 and long bone fracture, but not with mortality. Although there is no general agreement on the cutoff point for defining the severity of COVID-19, most studies used a cutoff value of ≥ 10 mg/L. Our analysis showed the diagnostic value of serum CRP ≥ 10 mg/L for the cumulative severe course of COVID-19, as most patients had CRP levels above this mark on day 3 of treatment. Previous studies attempting to predict mortality in sepsis by the presence of elevated serum CRP have been inconclusive. A study found that elevated serum CRP was associated with 30-day mortality, whereas other studies have shown the opposite [6, 7]. These discrepancies may be caused by the different cut-off values used. In a study by Koozi et al. (2020), the cut-off value for elevated serum CRP was ≥ 1000 mg/L [4], while the study by Ryoo et al. (2020), the limit point ≥ 140 mg/l was used [9]. Liu F. et al. (2020) proposed a cut-off value of ≥ 41.8 mg/L for predicting a severe form of COVID-19 [6]. In our study, serum CRP cut-off values varied widely, with the lowest and highest values being >3 mg/L and >100 mg/L, respectively. These findings reflect the urgent need to find an optimal serum CRP threshold for predicting COVID-19. The time period for measuring serum CRP was critical in light of the timely increase in serum CRP that peaks 72 hours after the initial strokes. Despite its value in predicting a poor outcome in COVID-19, it should be noted that various factors may influence serum CRP levels, including age, sex, smoking status, weight, lipid levels, blood pressure, and liver damage [6]. These factors should be taken into account when interpreting serum CRP levels. In addition, recent data have shown that serum CRP levels can also be used to monitor progression and improvement in patients with COVID-19.

The peptide precursor of the hormone calcitonin, PCT, has been widely investigated as a promising biomarker for the initial investigation of bacterial infection. Elevated serum PCT is often found in patients with sepsis and septic shock [5]. Although it is still controversial whether PCT can accurately distinguish between bacterial and viral pneumonia, PCT-guided therapy of acute respiratory infections has been found to reduce antibiotic exposure and side effects and improve survival rates [3]. Bacterial infections trigger extrathyroidal PCT synthesis, which is actively supported by elevated levels of IL-6, IL-1 β , and TNF- α , while viral infections inhibit PCT production via interferon- γ [2]. This explains why serum PCT concentrations remain normal in uncomplicated cases of COVID-19, while elevated values may indicate bacterial co-infection in severe cases [7]. In this study, we found that elevated serum PCT was associated with the presence of long bone fracture and severe COVID-19.

Conclusions

1. The dynamics of the CRP level in patients with fractures against the background of COVID-19 indicated that this inflammatory marker is not informative at the initial stage, however, starting from the 3rd day, a significant increase in the CRP level was noted with a subsequent drop in the level in the postoperative period on the 10th day of treatment.

2. The dynamics of the PCT level was approximately the same during all observation periods and did not reflect the changes that occurred in patients with long bone fractures against the background of COVID-19, which does not allow the use of this inflammatory marker in the clinical diagnosis of the course of COVID-19 in patients with long bone fractures bones.

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FEATURES OF BLOOD GAS COMPOSITION AND ACID-BASE BALANCE IN CHILDREN WITH ACUTE RESPIRATORY FAILURE CAUSED BY THE NEW CORONAVIRUS SARS-CoV-2

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A comprehensive examination of 61 children with severe acute respiratory infections made it possible to establish that in patients with a coronavirus infection caused by SARS-CoV2, upon admission to the Department of Anesthesiology and Intensive Care, more pronounced hypoxemia was probably registered more often. It was reflected statistically significant risks of SpO₂ reduction < 92 % (odds ratio 3.9), pO₂ < 41 mm Hg. and ctO₂ < 14 mL/dL (odds ratio 2.9). Patients with symptoms of COVID-19 had high levels of acid-base disorders, with metabolic and respiratory alkalosis being the most common variants of the disorder. It has been established that there are likely chances of having COVID-19 in hospitalized children in the presence of HCO₃ > 25 mmol/l (odds ratio – 5.4), Hct > 40 (odds ratio – 4.9), TCO₂ > 30 mmol/l (odds ratio – 3.4).

Key words: respiratory failure, COVID-19, children, blood gas composition

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ОСОБЛИВОСТІ ГАЗОВОГО СКЛАДУ КРОВІ ТА КИСЛОТНО-ЛУЖНОЇ РІВНОВАГИ У ДІТЕЙ ІЗ ГОСТРОЮ ДИХАЛЬНОЮ НЕДОСТАТНІСТЮ, СПРИЧИНЕНОЮ НОВИМ КОРОНАВІРУСОМ SARS-CoV2

Проведене комплексне обстеження 61 дитини з важкими гострими респіраторними інфекціями дозволило встановити, що у пацієнтів, хворих на коронавірусну інфекцію спричинену SARS-CoV2 при поступленні до відділення анестезіології та інтенсивної терапії вірогідно частіше реєстрували виразнішу гіпоксемію, яку відображали статистично достовірні ризики зниження SpO₂ < 92 % (співвідношення шансів 3,9), pO₂ < 41 мм рт.ст. та ctO₂ < 14 мл/дл (співвідношенням шансів 2,9). Пацієнти з симптомами COVID-19 мали високий рівень кислотно-лужних розладів, метаболічний та респіраторний алкалоз були найпоширенішими варіантами порушень. Встановлено, вірогідні шанси наявності COVID-19 у госпіталізованих дітей за наявності HCO₃ > 25 ммоль/л (співвідношення шансів – 5,4), Hct > 40 (співвідношення шансів – 4,9), TCO₂ > 30 ммоль/л (співвідношення шансів – 3,4).

Ключові слова: дихальна недостатність, COVID-19, діти, газовий склад крові

The work is a fragment of the research project "Modern epidemiological, clinical-paraclinical and diagnostic features of the most common inflammatory diseases of infectious and non-infectious nature in children", state registration No. 0122U002208.

According to the WHO definition, the acute infectious disease caused by the new SARS-CoV-2 coronavirus was named "severe acute respiratory syndrome", which acquired the characteristics of a coronavirus pandemic or COVID-19 [8]. To date, the results of longitudinal observations on a global scale have been accumulated, which showed a sufficiently high susceptibility of the subpopulation of children and adolescents to the new SARS-Co-V-2 coronavirus with a mild or asymptomatic course that is much more frequent than in adults. As a result, according to some researchers, at the beginning of the pandemic, it was believed that children were not susceptible to COVID-19. As a result, the frequency of infection was underestimated due to the low coverage of pediatric patients with SARS-CoV-2 testing [3]. At the same