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CLINICAL COURSE AND PATHOMORPHOLOGICAL FEATURES OF CORONAVIRUS DISEASE COMORBID TO COMMUNITY-ACQUIRED PNEUMONIA AND ANEMIC CONDITIONS

Monograph

(Edited by Professor O.S. Khukhlina)

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This monograph presents epidemiological, clinical, and pathomorphological features of the complicated course of coronavirus disease, as well as pathogenetic aspects of the development of community-acquired pneumonias of viral and viral-bacterial etiology and anemic conditions. The structure of comorbid pathology in community-acquired pneumonias of viral and viral-bacterial etiology is described.

The monograph is for physicians, post-graduate students, higher medical education trainees, and PhD students.

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INTRODUCTION

The relevance of the topic is determined by the significant prevalence of coronavirus disease (COVID-19) worldwide and in Ukraine since 2020, as well as the high mortality associated with its complicated course. More than four years after the onset of the COVID-19 pandemic caused by the SARS-CoV-2 virus, research continues to investigate the features of its clinical presentation, to search for new diagnostic and therapeutic approaches, and to study its long-term consequences. Despite the substantial amount of available research, accumulated clinical experience, and the development of vaccines and antiviral agents, the pandemic has left numerous clinical, biological, social, and ethical challenges. Today, the study of COVID-19 has not lost its relevance; on the contrary, it has shifted from the acute response phase to a new stage focused on medical analysis, adaptation of healthcare systems, and forecasting of long-term outcomes.

The overall relevance of COVID-19 research is driven by its scale, variability, multisystem involvement, potential to cause severe disease in certain population groups, and the possibility of emerging new viral variants capable of provoking another pandemic wave. SARS-CoV-2 has become one of the most thoroughly studied pathogens in the history of not only virology but also immunology, epidemiology, and molecular biology.

The primary clinical manifestation of COVID-19 involving the lower respiratory tract is viral community-acquired pneumonia or early mixed viral-bacterial pneumonia. Currently, there is a decline in the incidence of community-acquired pneumonia (CAP) in the general population, including its association with SARS-CoV-2 infection – either pneumonia arising on the background of viral disease (CAP-S) or occurring shortly after COVID-19 (primary viral-bacterial or secondary bacterial pneumonia). At the same time, a substantial proportion of severe CAP cases is observed among patients with comorbidities such as obesity, diabetes mellitus, heart failure, chronic kidney disease (CKD), and liver diseases.

The COVID-19 epidemic, caused by the SARS-CoV-2 virus, began in December 2019 in Wuhan, Hubei Province, People's Republic of China, and was declared a pandemic by the World Health Organization (WHO) on 11 March 2020. On 30 December 2019, a report on cases of "pneumonia of unknown origin" was released by the Chinese Medical Administration and the Medical Administration of the Wuhan Municipal Health Commission. On 9 January 2020, WHO confirmed that a novel coronavirus had been isolated from one of the hospitalized patients. On the same day, the European Centre for Disease Prevention and Control issued its first risk assessment.

During the pandemic, 704.75 million cases were recorded globally, and more than 7 million people died. According to the Ministry of Health of Ukraine and the National Security and Defense Council, as of 13 April 2024, a total of 5,557,995 cases of SARS-CoV-2 infection (13.5%) had been confirmed in Ukraine, of which 112,418 deaths (2.0%) and 5,445,577 recoveries (98.0%) were reported. At the peak of the epidemic, the overall case-fatality rate was approximately 2%, and 5-20% of patients required

hospitalization, of whom 10-30% needed intensive care, creating a substantial burden on the healthcare system. Community-acquired pneumonia (CAP) developed in 35-40% of individuals with COVID-19 in a mild form, in 15-28% in a moderate form, in 10-15% as severe pneumonia requiring intensive care with oxygen support, and in 5% as a critical form with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiple organ failure involving the kidneys, liver, and myocardium.

In May 2023, WHO announced that COVID-19 was no longer a Public Health Emergency of International Concern; however, it also acknowledged that the pandemic had not yet fully ended. Therefore, early diagnosis of CAP associated with COVID-19, as well as the study of its clinical features to predict severe disease and prevent complications, remains a priority for public health and underlines the need for further scientific research in this field. At the same time, a review of available literature indicates a limited number of studies specifically comparing the clinical course of community-acquired pneumonia caused by COVID-19 with pneumonia of other viral-bacterial etiologies.

One of the major achievements to date has been the elucidation of the pathogenic mechanisms underlying the course of COVID-19. It has been clearly established that the virus enters the human body through angiotensin-converting enzyme receptors (ACE2), which are expressed in the epithelial cells of the lungs, cardiomyocytes, vascular endothelium, the gastrointestinal tract, kidneys, and other organs and tissues. After entering the cell, the virus triggers a cascade of immune reactions that may lead to a cytokine storm, alveolar injury, endothelial dysfunction, microvascular thrombosis, and multiorgan failure. A particularly severe disease course is observed in patients with comorbidities such as cardiovascular diseases, type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), oncologic conditions, and immunosuppressive states.

Among the most significant scientific achievements related to COVID-19 are the development of modern highly effective vaccines, which substantially reduced the economic burden of the disease, the advancement of direct-acting antiviral agents, and improvements in early diagnostic methods and clinical monitoring of disease severity.

A major success of modern medicine has been the development and global implementation of COVID-19 vaccines. Vaccination has significantly decreased hospitalization rates and mortality associated with COVID-19, particularly among high-risk groups. The development of mRNA vaccines (Pfizer-BioNTech, Moderna) represented a breakthrough in biotechnology. However, alongside these achievements, humanity continues to face new challenges: maintaining adequate immune protection amid declining antibody levels, the emergence of new viral variants (such as Omicron and its subvariants), the high prevalence of Long COVID among recovered individuals, and the need to prevent the long-term consequences of SARS-CoV-2 infection.

It is well established that SARS-CoV-2 can induce a prolonged post-infectious syndrome known as post-COVID or Long COVID. This condition includes a constellation of symptoms persisting for more than 12 weeks after the acute phase of

the disease, such as chronic fatigue, cognitive impairment, dyspnea, myalgia, and anxiety disorders. The study of Long COVID remains highly relevant, particularly regarding its potential mechanisms, including viral persistence, autoimmune responses, alterations in gut microbiota, and microcirculatory endothelial injury. The absence of unified treatment strategies for Long COVID represents an urgent and unresolved clinical issue requiring further investigation.

The impact of COVID-19 on pre-existing chronic diseases remains insufficiently investigated to date. The assumptions regarding the ability of the virus to trigger the manifestation of diabetes mellitus, heart failure, chronic kidney disease, or mental disorders have not yet been fully clarified. There is reason to believe that SARS-CoV-2 infection may initiate a cascade of metabolic changes and vascular remodeling of various calibers, which may become clinically evident only years later.

The study of the immune response to SARS-CoV-2 remains an important area of scientific inquiry. Particularly relevant are investigations into the role of T-cell immune memory, immune responses in immunosuppressed patients or transplant recipients, and cross-immunity between different viral variants. These aspects are essential for optimizing future vaccination strategies, determining the need for revaccination, and developing universal vaccines.

Modern approaches to the treatment of COVID-19 also require continuous monitoring and refinement. During the acute phase of infection, the use of antiviral drugs (remdesivir, molnupiravir, nirmatrelvir/ritonavir), glucocorticoids, anti-cytokine therapy (tocilizumab), and anticoagulants remains relevant. However, the effectiveness and safety of these therapeutic classes depend on the timing of their administration, patient phenotype, and comorbid conditions. It remains insufficiently studied, yet critically important, which biomarkers can predict disease progression, complications, or therapeutic response.

Beyond medical aspects, the COVID-19 pandemic has revealed systemic vulnerabilities within healthcare systems, including shortages of medical resources, insufficient preparedness for large-scale infectious threats, the necessity of integrating telemedicine into routine clinical practice, and the need to advance medical informatics and multidisciplinary patient care. These issues will remain subjects of continued analysis and optimization for healthcare administrators at all levels.

Among the unresolved scientific issues related to COVID-19, particular attention must be given to its impact on the hematologic system, especially the development of anemic states during SARS-CoV-2 infection. Clinical observations indicate that some patients with COVID-19 develop normocytic or hypochromic anemia, which may result from systemic inflammation, suppression of erythropoiesis, or disruptions in iron metabolism. Activation of pro-inflammatory cytokines, particularly IL-6, is known to stimulate hepcidin production, which blocks iron release from macrophages and reduces intestinal absorption, ultimately leading to anemia of chronic disease. Additional hypotheses include immune-mediated erythrocyte destruction and bone marrow suppression caused by hypoxemia, intoxication, or direct viral damage to hematopoietic

tissues. These pathogenetic mechanisms require further investigation to develop effective therapeutic approaches for patients with comorbid anemic disorders.

Thus, the relevance of studying COVID-19 today is determined by the multifactorial nature of this disease and its potential long-term impact on the human body, society, healthcare systems, and science as a whole. Despite the unquestionable control over the acute phase of the pandemic, many aspects of the pathogenesis, diagnosis, treatment, prevention, and social consequences of coronavirus infection remain unresolved. Future research must be interdisciplinary, multicenter, and aimed both at addressing short-term clinical challenges and at preventing possible long-term health consequences for the global population.

The aim of our study was to determine age-related and gender-specific characteristics of the incidence and clinical course of viral community-acquired pneumonia caused by SARS-CoV-2 infection, compared with community-acquired viral–bacterial pneumonias of other etiologies among residents of the Chernivtsi region; to analyze the structure and features of mortality depending on sex, age, comorbidities, and disease severity; to investigate the frequency, structure, and pathogenetic mechanisms of anemia in patients with COVID-19; and to evaluate the morphofunctional and pathomorphological features of the infectious process in the presence of concomitant anemia of varying severity.

Research objectives:

- To determine sex- and age-related characteristics of the incidence of moderate community-acquired pneumonia caused by SARS-CoV-2 infection by comparing it with the course of community-acquired viral–bacterial pneumonias (CABP) of other etiologies in patients hospitalized in the Infectious Diseases and Pulmonology Departments of the Chernivtsi Regional Clinical Hospital
- To assess the intensity and frequency of clinical symptoms of moderate CAP caused by COVID-19 compared with CABP of other etiologies
- To evaluate changes in pulmonary function (based on spirometry), radiological findings of the chest, and pulse oximetry parameters in patients with moderate CAP associated with SARS-CoV-2, compared with CABP of different origins
- To analyze changes in biochemical markers of inflammation (CBC, CRP, fibrinogen, ferritin), markers of hepatic and renal injury, as well as laboratory findings (sputum analysis, sputum culture with identification of bacterial flora and antibiotic susceptibility) in patients with SARS-CoV-2-associated CAP compared with other forms of CABP
- To analyze the structure of comorbid conditions in patients with moderate SARS-CoV-2-associated CAP compared with CABP of other etiologies
- To determine the frequency of anemia among hospitalized patients with COVID-19
- To evaluate age- and gender-specific features of anemia of varying severity in patients with COVID-19
- To investigate the effect of concomitant anemia on the development of complications of COVID-19, particularly viral-bacterial pneumonia

- To assess the morphological and biochemical characteristics of anemia in patients with COVID-19 (type of anemia, iron and ferritin levels)
- To analyze the potential relationship between the severity of anemia, procalcitonin levels, and length of hospital stay in patients with COVID-19

Object of the study: community-acquired pneumonia associated with COVID-19 of moderate severity; viral-bacterial pneumonias of other etiologies of moderate severity; patients with COVID-19 presenting with anemic conditions of various origins

Subject of the study: sex- and age-related features of the disease; clinical characteristics of community-acquired pneumonia depending on its etiology (including SARS-CoV-2); radiographic, spirometric, and pulse-oximetry changes; functional status of the liver and kidneys; intensity of the inflammatory response; etiological structure of bacterial co-infections; structure of comorbid conditions; clinical features of COVID-19 in patients with concomitant anemia.

Research methods: clinical methods; laboratory tests (complete blood count, sputum examination, sputum culture with identification of microflora and antibiotic susceptibility), biochemical tests (serum activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT); blood levels of urea, creatinine, bilirubin and its fractions, C-reactive protein (CRP), ferritin, fibrinogen); instrumental methods (radiography, spirometry, pulse oximetry); statistical analysis.

Scientific novelty of the obtained results. Based on the study of the epidemiology and clinical features of community-acquired pneumonia associated with COVID-19 of moderate severity, and its comparison with community-acquired viral-bacterial pneumonias (CABP) of other etiologies among patients hospitalized in the Infectious Diseases and Pulmonology Departments of the Chernivtsi Regional Clinical Hospital, the following findings were established. Women were more frequently affected by SARS-CoV-2–associated pneumonia (CAP-S), and they more often presented with bilateral lung involvement, pleural reactions, and subsequent development of diffuse pneumofibrosis. The course of COVID-19 was characterized by a higher frequency of complaints of intense chest pain during breathing and coughing, fever, anosmia, severe sore throat with odynophagia, progressive dyspnea, myalgia, asthenia, severe headache at disease onset, short episodes of syncope, nausea, and diarrhea ($p<0.05$).

Patients with CAP-S significantly more often demonstrated prolonged fever >38.5°C, heart rate >90 bpm, respiratory rate >25/min ($p<0.05$), as well as lower oxygen saturation values of 90-92% ($p<0.05$). Laboratory abnormalities more frequently included leukopenia, lymphopenia, thrombocytopenia, and elevated ESR ($p<0.05$). Inflammatory activity was higher due to hyperfibrinogenemia, hyperferritinemia, and CRP >20 mg/L ($p<0.05$), which exceeded corresponding values in patients with CABP.

Among COVID-19 patients with pneumonia, acute reactive hepatitis of mild or moderate activity, acute kidney injury, and progression of pre-existing chronic kidney disease occurred more frequently. Radiographically, patients with CAP-S demonstrated bilateral lung involvement 1.9 times more often, predominantly affecting lower and

middle lung zones; ground-glass opacities with enhanced reticular pattern, areas of consolidation, diffuse fibrotic lung changes, and pleural inflammatory reactions were visualized 6.3 times more often ($p<0.05$).

The course of CABP was more frequently accompanied by bronchial obstruction ($p<0.05$), whereas CAP-S was predominantly associated with restrictive ventilatory abnormalities caused by bilateral infiltrative lung involvement and development of pneumosclerosis. The frequency of bacterial and fungal co-infections and superinfections in CAP-S was significantly lower (17.0%) compared to CABP (52.0%), and the spectrum of isolated microorganisms differed substantially ($p<0.05$).

Patients with CAP-S more often exhibited risk factors for severe pneumonia, such as overweight, obesity, hyper- and dyslipidemia, and had a markedly greater prevalence of comorbid conditions including type 2 diabetes mellitus, arterial hypertension, coronary artery disease, acute myocarditis, heart failure, chronic kidney disease, metabolic syndrome, acute reactive hepatitis, pancreatitis, and impaired glucose tolerance. In contrast, patients with CABP more commonly had smoking history, bronchial asthma, and chronic obstructive pulmonary disease (COPD).

Practical significance of the obtained results. Based on the results of a comprehensive analysis of age-, sex-, and clinical characteristics of SARS-CoV-2–associated community-acquired pneumonia (CAP-S), the understanding of clinical and pathogenetic features, mechanisms of progression, and the structure of comorbid conditions that contribute to a more severe course of pneumonia has been expanded. Implementation of the study findings into clinical practice has improved the identification of risk factors for complicated CAP in the setting of COVID-19.

Based on the obtained research data, clinical and laboratory predictors of severe COVID-19 in patients with concomitant anemia were identified, providing a rationale for early recognition of such individuals as a high-risk group. The performed analysis supports the need to refine risk stratification and to individualize treatment strategies, taking into account hemoglobin levels, ferritin and serum iron concentrations, and procalcitonin. The results may be applied in clinical practice to optimize the management of patients with COVID-19 and concomitant anemia, which may help reduce the incidence of complications and shorten the duration of hospitalization.

CHAPTER 1

CORONAVIRUS INFECTIONS: HISTORICAL ASPECTS, BIOLOGY OF THE PATHOGEN, PATHOMORPHOLOGY, PATHOGENESIS, AND CLINICAL MANIFESTATIONS OF COVID-19 IN PATIENTS WITH COMORBID CONDITIONS (LITERATURE REVIEW)

1.1. Historical aspects of coronavirus research and the evolution of their epidemiological significance

Coronaviruses (family Coronaviridae) have been known to humanity since the second half of the twentieth century; however, their true significance as potentially dangerous pathogens became evident only at the beginning of the twenty-first century. The first scientifically documented mentions of coronaviruses date back to the 1960s, when British and American researchers David A. J. Tyrrell and Malcolm L. Bynoe of the Medical Research Council (United Kingdom) independently identified two viruses that caused symptoms resembling the common cold. These were HCoV-229E and HCoV-OC43-representatives of the alpha- and beta-coronaviruses, respectively, isolated from nasopharyngeal samples of patients with mild respiratory illnesses. The morphological feature of these viruses – crown-like spike projections on the virion surface – gave rise to the name of this group of infectious agents, “coronaviruses” (from the Latin corona, meaning “crown”).

In the following decades, coronaviruses were regarded as relatively harmless pathogens causing uncomplicated forms of acute respiratory viral infections, primarily in children and individuals with weakened immunity. Their contribution to the overall structure of seasonal viral morbidity was relatively small, not exceeding 10-15%, and the clinical manifestations were mild – rhinorrhea, mild cough, and low-grade fever. Consequently, scientific interest in this group of viruses remained limited. However, the emergence of new pathogenic strains capable of causing severe pneumonia and systemic involvement fundamentally changed scientific perspectives on these viruses.

The first major epidemiological outbreak caused by coronaviruses was recorded in 2002 in Guangdong Province, China, where an epidemic of Severe Acute Respiratory Syndrome (SARS) emerged. The causative agent of the pandemic was a novel betacoronavirus, SARS-CoV, transmitted from animals (likely civets or bats) to humans. This newly identified viral agent caused profound injury to the lower respiratory tract with a high risk of acute respiratory distress syndrome (ARDS), which often proved fatal. The virus spread rapidly beyond China, with the epidemic affecting more than 30 countries, including Canada, Vietnam, Singapore, and Hong Kong. A total of approximately 8,100 cases were registered, more than 770 of which resulted in death, corresponding to a case-fatality rate of around 9.6% (https://www.who.int/publications/m/item/summary-of-probable-sars-cases-with-onset-of-illness-from-1-november-2002-to-31-july-2003). This became the first major

warning to the medical community regarding the potential danger posed by novel coronavirus strains with high epidemic potential.

Ten years later, in 2012, Saudi Arabia reported a case of a new disease – Middle East Respiratory Syndrome (MERS), caused by the MERS-CoV coronavirus. Dromedary camels were identified as the primary source of infection, while bats were considered the initial reservoir. MERS-CoV had lower transmissibility within the population but significantly higher lethality (over 35%). In most cases, the disease presented with severe pneumonia, ARDS, and acute renal failure. Although this outbreak did not reach global proportions, it once again demonstrated that zoonotic coronaviruses pose a serious threat to human health.

A key turning point in the history of coronavirus epidemics was the emergence of a new pathogenic strain – SARS-CoV-2 – at the end of 2019 in Wuhan, China. The first reports described cases of atypical pneumonia of unknown origin. By January 2020, the genome of the probable new pathogen had already been sequenced, revealing close phylogenetic relatedness to SARS-CoV. The virus demonstrated efficient human-to-human transmission via respiratory droplets as well as contact with contaminated surfaces. A high level of contagiousness, asymptomatic carriage, a prolonged incubation period (up to 14 days), and a broad spectrum of clinical manifestations facilitated its rapid spread both within China and globally.

In March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic. This was the first pandemic caused by a coronavirus and the first in modern history to have a simultaneous impact on every continent, affecting more than 200 countries. The consequences were unprecedented: health-care system collapse, overwhelming burden on medical personnel, shortages of essential resources, and increased mortality among vulnerable population groups. At the same time, the pandemic triggered a global economic recession, widespread social disruption, restrictions on population mobility, declines in educational outcomes, and deterioration in mental health due to prolonged isolation.

Particularly concerning were the recurrent waves of infection and the emergence of new viral variants with mutations in the spike (S) protein, which reduced the effectiveness of natural immunity and vaccines. In response, governments imposed strict quarantine measures, implemented large-scale testing programs, travel restrictions, and introduced digital tools for epidemiological surveillance. Meanwhile, vaccine development and the search for effective therapeutic strategies progressed at unprecedented speed. By December 2020, the first mRNA vaccines were authorized for emergency use, marking a historic breakthrough in immunoprophylaxis.

The COVID-19 pandemic compelled the scientific community to reconsider the role of coronaviruses within the overall structure of infectious diseases. From a group of “secondary” pathogens, they have transformed into one of the most extensively investigated classes of viruses. Large-scale global research initiatives were launched to study their evolution, interspecies transmission barriers, tropism to various organs and tissues, mechanisms of immune response, and the potential for specific immunotherapy and prophylaxis. COVID-19 infection triggered not only a medical crisis, but also a

political, economic, and social one, revealing the vulnerability of modern civilization to emerging biological threats.

1.2. Biological properties and taxonomy of coronaviruses. Distinctive features of SARS-CoV-2 as the etiological agent of the COVID-19 pandemic

Coronaviruses belong to the family Coronaviridae, which, together with the families Arteriviridae, Roniviridae and Mesoniviridae, is included in the order Nidovirales. Members of this family are single-stranded RNA viruses with a positive-sense genome. They are characterized by a remarkably large genomic length (nearly 30 kilobases), complex structural organization, and a high frequency of recombination events, which determines their substantial genetic variability and high adaptive potential. Morphologically, coronaviruses have a spherical or oval shape; their virions are surrounded by a lipid envelope, on the surface of which club-shaped glycoprotein spikes are located, providing the characteristic corona-like appearance in electron microscopy.

The Coronaviridae family is divided into four major genera – Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus – according to phylogenetic analysis of their nucleotide sequences (https://ictv.global/taxonomy). These genera differ both in host tropism and in pathogenic properties. Alpha- and betacoronaviruses infect mammals, including humans, whereas gamma- and deltacoronaviruses predominantly infect birds and certain other animal species, and to date no evidence exists suggesting their ability to infect humans.

Among the coronaviruses potentially hazardous to humans, the most widespread are the so-called seasonal or endemic strains, which typically cause uncomplicated acute respiratory infections. These include four major representatives:

- ***HCoV-229E*** (alphacoronavirus) – one of the earliest identified human coronaviruses, which circulates continuously in the population and causes mild common-cold-like illnesses;
- ***HCoV-NL63*** (alphacoronavirus) – detected in 2004 in the Netherlands; it causes rhinitis, pharyngitis, laryngitis and may induce croup in children;
- ***HCoV-OC43*** (betacoronavirus) – closely related to bovine coronaviruses and is believed to have acquired the ability to infect humans through zoonotic transmission;
- ***HCoV-HKU1*** (betacoronavirus) – discovered in 2005 in Hong Kong; it is also associated with mild upper respiratory tract infections.

These viruses typically exhibit seasonal activity (predominantly in the autumn-winter period), are transmitted via respiratory droplets and contact pathways, and in most cases cause short-lived illness without severe consequences. They have achieved global circulation, and due to their limited immunogenicity, repeated infections throughout life are common.

A distinct category is represented by highly pathogenic coronaviruses, all of which belong to specific subgenera within the genus Betacoronavirus. This group includes:

- ***SARS-CoV*** (Severe Acute Respiratory Syndrome Coronavirus) – first identified in 2002 in China. Bats are considered the most probable natural reservoir, whereas civets served as an intermediate host. The virus causes severe lower respiratory tract disease with an estimated case fatality rate of approximately 10%
- **MERS-CoV** (Middle East Respiratory Syndrome Coronavirus) – detected in 2012 in Saudi Arabia. Dromedary camels are regarded as the primary source of human infection, while bats constitute the natural reservoir. The infection is characterized by a markedly high fatality rate (over 35%) and a severe clinical course with acute respiratory failure and frequent renal impairment
- **SARS-CoV-2** (Severe Acute Respiratory Syndrome Coronavirus 2) – the causative agent of the COVID-19 pandemic. Its genetic material demonstrates strong phylogenetic similarity to bat coronaviruses. SARS-CoV-2 is distinguished by its high human-to-human transmissibility, potential for asymptomatic carriage, and wide clinical spectrum. While respiratory droplet transmission is predominant, contact and aerosol routes are also possible

SARS-CoV, MERS-CoV, and SARS-CoV-2 share fundamental genomic structural features, yet they differ significantly in clinical severity, pathogenic mechanisms, and epidemiological impact. These viruses illustrate the high adaptive capacity of zoonotic coronaviruses to human hosts. Events of cross-species transmission highlight the complexity of evolutionary processes that give rise to novel pathogens with considerable pandemic potential. For these reasons, this subgroup of coronaviruses remains at the forefront of global virological research.

Thus, the classification of coronaviruses reflects both their biological diversity and their potential threat to human health. Ranging from seasonal respiratory pathogens to agents of severe systemic infections, coronaviruses encompass a broad spectrum of clinical manifestations. Comprehensive study of their taxonomy, structural organization, and evolutionary mechanisms is essential for epidemiological forecasting, biosafety planning, and the development of effective vaccination strategies in the context of global population mobility and rapidly changing environmental conditions.

SARS-CoV-2, the causative agent of COVID-19, belongs to the subgenus Sarbecovirus, genus Betacoronavirus, family Coronaviridae. It is an enveloped, single-stranded, positive-sense RNA virus measuring approximately 80–120 nanometres in diameter (Fig. 1). SARS-CoV-2 possesses one of the largest genomes among all known RNA viruses: roughly 29,900 nucleotides encoding both structural and non-structural proteins. Its unique morphological and molecular features underpin its tissue tropism, high infectivity, and pathogenic potential, which collectively manifest in the wide range of clinical presentations observed in COVID-19.

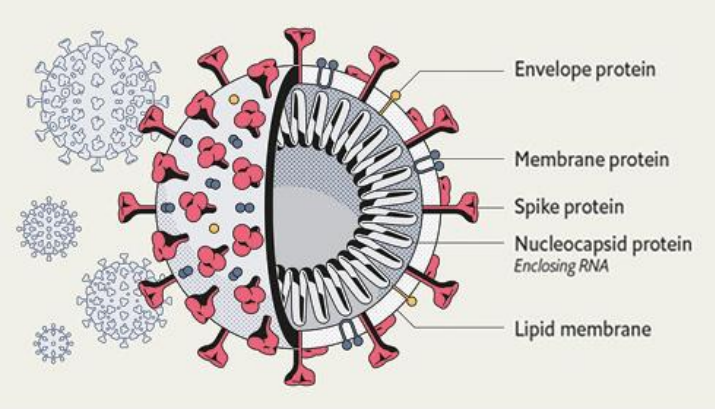


Fig. 1. Structure of the coronavirus (https://umj.com.ua/uk/publikatsia-175048-koronavirus-ta-inshi-emerdzhentni-infektsiyi)

The external structure of the virus is formed by a lipid envelope into which three types of membrane proteins are embedded: S (spike), M (membrane), and E (envelope). Beneath the envelope lies the nucleocapsid protein (N), which binds the viral RNA and stabilizes it during the assembly of new virions. The most clinically significant component in the infection process is the S protein – a spike glycoprotein that forms crown-like protrusions on the virion surface. It is responsible for attachment to target cells and the initiation of fusion between the viral envelope and the cellular membrane.

Structurally, the S protein consists of two subunits, S1 and S2. The S1 subunit contains the receptor-binding domain (RBD), which recognizes angiotensin-converting enzyme 2 (ACE2) – the main receptor expressed on the surface of human epithelial cells, particularly in the lungs, intestines, kidneys, heart, and blood vessels. The S2 subunit mediates the fusion of viral and cellular membranes.

After the virus attaches to the target cell via S1 binding to ACE2, activation of the S protein occurs through the action of the host cell protease TMPRSS2, which cleaves the protein at the S1/S2 junction. This enables the virus to fuse with the host cell membrane and enter its cytoplasm. Subsequently, the replication cycle begins within the cytoplasm: the released viral RNA is translated into polyproteins that are processed into functional proteins, including RNA polymerase, helicase, protease, and elements of the replication-transcription complex. In parallel, new RNA copies are synthesized, and virions are assembled together with the N protein. The assembled viral particles are then exocytosed from the cell, leading to its destruction and further spread of infection to adjacent cells.

Genetically, SARS-CoV-2 encodes four structural proteins (S, M, E, N) and 16 nonstructural proteins formed through the processing of two large open reading frames (ORF1a and ORF1b). These proteins perform essential functions ranging from inhibition of the host antiviral response to replication of the viral genome. It is precisely this complex genetic organization and high plasticity of SARS-CoV-2 that underlie its strong adaptive capacity, facilitating its rapid global spread and the emergence of new variants.

The relationship between the morphological structure of the virus and the clinical manifestations of coronavirus infection is fundamental for understanding the pathogenesis of the disease. First, the expression of the ACE2 receptor, which the virus uses to enter host cells, determines its tropism for different tissues. The highest ACE2 expression is observed in type II alveolar epithelial cells, which explains the frequent development of severe lung injury. In addition, ACE2 is present in vascular endothelial cells, cardiomyocytes, renal parenchymal cells, and the gastrointestinal tract, which accounts for the multi-organ nature of the clinical presentation – from pneumonia to enteritis, nephritis, and viral myocarditis.

Second, the intensive binding of the S protein to ACE2 leads to a reduction in the functional activity of this receptor, resulting in dysregulation of the renin-angiotensin system: accumulation of angiotensin II and deficiency of angiotensin-(1-7), which normally exerts vasodilatory and anti-inflammatory effects. Consequently, endothelial dysfunction develops, vascular permeability increases, and pro-inflammatory cytokines are activated. Thus, the interaction between the S protein and ACE2 triggers a cascade of reactions leading to pulmonary edema, localized hypoxia, and marked inflammatory infiltration.

Third, the interaction of the virus with the immune system is driven by the activity of SARS-CoV-2 nonstructural proteins, which inhibit interferon responses, block antigen-presenting pathways, and stimulate the production of pro-inflammatory cytokines. This immune imbalance may progress to a cytokine storm – one of the key mechanisms underlying severe COVID-19. In such patients, systemic inflammation, endothelial injury, and coagulopathies, including thrombosis and thromboembolism, develop, directly correlating with the presence of the virus in ACE2-rich tissues.

The structural features of the virus also determine its variability. The S-protein is the primary target for neutralizing antibodies; therefore, mutations within the receptor-binding domain (RBD) can alter the effectiveness of the immune response and facilitate the emergence of new variants. Mutations that increase the affinity of the S-protein for ACE2 enhance the infectivity and pathogenic potential of the virus, whereas mutations that modify its antigenic properties may reduce vaccine effectiveness. This has been confirmed in studies of the Alpha, Delta, and Omicron variants, which demonstrated increased transmissibility, immune-escape properties, and partial resistance to monoclonal antibody therapies.

Thus, the morphological and genetic structure of SARS-CoV-2 directly determines its epidemiological characteristics, mechanisms of host-cell entry, and broad spectrum of clinical manifestations. The virus exhibits a remarkable ability to adapt rapidly, display broad tissue tropism, modulate immune responses, and induce systemic organ dysfunction, making it one of the most consequential pathogens of the modern era. Understanding these features is essential for the development of effective strategies for diagnostics, treatment, prevention, and control of the COVID-19 pandemic.

1.3. COVID-19 in patients with comorbid conditions: pathogenesis, clinical features, and prognosis

COVID-19, caused by the SARS-CoV-2 virus, remains a major global challenge for modern healthcare systems, leading to substantial clinical, epidemiological, and socio-economic consequences. Understanding the clinical characteristics of the disease, both in individuals with an isolated, uncomplicated course and in those with underlying comorbid conditions, is essential for improving diagnostic accuracy and developing optimal strategies for treatment, clinical management, prevention of complications, and mitigation of long-term sequelae.

An isolated, uncomplicated course of COVID-19 is most frequently observed in young individuals with generally good baseline health. Typical symptoms in such cases include fever (usually 37.5-38.5°C), dry cough occasionally accompanied by small amounts of mucous sputum, sore throat, general malaise, headache, and myalgia; less commonly, nausea or diarrhea may occur. A proportion of patients develop anosmia (loss of smell) and ageusia (loss of taste), which are considered characteristic features of COVID-19.

On physical examination, these patients typically present with moderate fever, and less frequently with subfebrile temperatures. Dyspnea is usually absent, with oxygen saturation (SpO_2) maintained at 95-98%. Respiratory rate generally remains within normal limits (up to 20 breaths per minute). Auscultation of the lungs may reveal occasional dry crackles. Overall, the general condition of these patients remains satisfactory, and hospitalization is not required unless complications arise or clinical deterioration occurs.

In patients with concomitant chronic diseases of internal organs, the clinical presentation exhibits several distinguishing features. Individuals with conditions such as arterial hypertension, type 2 diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, malignancies of various localizations, as well as elderly patients, are at substantially increased risk of developing a severe course of COVID-19. In this population, viral infection is more frequently complicated by concomitant viral pneumonia, severe respiratory failure, and thromboembolic events.

In contrast to the isolated course of the disease, clinical manifestations in patients with comorbidities are more pronounced and clinically threatening. Body temperature often exceeds 38.5°C and is accompanied by marked systemic intoxication, profound fatigue, anorexia, and mixed-type dyspnea. In severe cases, mental confusion, hypotension, and tachycardia may occur. Oxygen saturation (SpO_2) declines below 94%, indicating impaired oxygenation and necessitating oxygen supplementation.

On physical examination, these patients may exhibit moist crackles and clinical signs of focal or diffuse pneumonia. Computed tomography findings typically confirm pulmonary parenchymal involvement, often presenting as bilateral “ground-glass” opacities with predominant changes in the basal lung segments. The lung involvement index frequently exceeds 15 points.

The combined course of COVID-19 and type 2 diabetes mellitus (T2DM) is characterized by a substantially more severe clinical presentation, an increased risk of complications, and higher mortality. Patients with T2DM belong to a high-risk group for SARS-CoV-2 infection, which is explained by the coexistence of metabolic and immune dysfunctions inherent to diabetes and the pathophysiological alterations induced by the viral infection itself. A key underlying reason for the more severe clinical course of COVID-19 in diabetic patients is the presence of chronic systemic inflammation characteristic of T2DM. These individuals exhibit elevated baseline levels of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), which amplify the development of the so-called cytokine storm in COVID-19. Hypercytokinemia may lead to endothelial dysfunction, activation of procoagulant pathways, enhanced thrombus formation, and ultimately multiorgan failure. Thus, COVID-19 is superimposed on an already disturbed metabolic milieu, significantly impairing the physiological systemic response to infection.

Another important mechanism underlying the combined course of the diseases is immune dysfunction in diabetes. Patients with T2DM demonstrate reduced activity of T-lymphocytes, neutrophils, and macrophages, which results in insufficient control of viral replication and a higher likelihood of secondary bacterial infection. Consequently, these patients face an increased risk of secondary bacterial pneumonia, prolonged recovery, and more frequent secondary septic complications, many of which may be fatal.

In addition, COVID-19 induces marked hormonal dysregulation, including elevated levels of cortisol and adrenaline due to physiological stress, which further exacerbates pre-existing insulin resistance. Under infectious stress, glycaemic control deteriorates (manifested by increased blood glucose levels and acute hyperglycaemia), which in turn further suppresses immune responses and promotes glycosylation of immunoglobulins and cell receptors. In some cases, hyperglycaemia progresses to diabetic ketoacidosis, necessitating urgent therapeutic intervention.

A particularly important role in the severe course of SARS-CoV-2 infection in patients with diabetes mellitus is attributed to alterations in the ACE2 receptor, which mediates viral entry into host cells. This receptor is expressed not only in the lungs but also in the pancreas, specifically in the β-cells of the islets of Langerhans. Theoretically, the virus may damage these cells, impairing insulin secretion and thereby contributing to decompensation of pre-existing diabetes or even triggering the onset of diabetes, a phenomenon reported in a subset of patients hospitalized with COVID-19.

Another significant risk factor in individuals with concomitant SARS-CoV-2 infection and diabetes is impaired microcirculation due to diabetic angiopathy. Combined with hypoxia, thrombosis, and endothelial dysfunction induced by COVID-19, this microvascular compromise significantly increases the risk of acute lung injury, cardiovascular complications (including myocardial infarction and arrhythmias), and acute kidney injury.

Thus, the mechanisms underlying the complicated course of COVID-19 in the presence of diabetes mellitus include chronic inflammation and cytokine imbalance,

impaired cellular immunity, hyperglycaemia and insulin resistance, potential β-cell injury, and the development of micro- and macrovascular dysfunction. Together, these factors create a “vicious circle” that necessitates strict glycaemic control, early prophylactic initiation of anticoagulation, timely and adequate oxygen therapy, and close clinical monitoring of patients with diabetes who are infected with SARS-CoV-2.

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, is a multisystem infection that affects not only the respiratory organs but also the cardiovascular system. In patients with pre-existing cardiovascular diseases, the course of COVID-19 is typically more severe due to the combined effects of direct viral injury and secondary mechanisms involving immune dysregulation, systemic inflammation, hypoxia, coagulopathy, and metabolic disturbances. At the same time, the infection itself can precipitate the onset or exacerbation of cardiovascular conditions in previously healthy individuals.

The mechanism underlying the mutual aggravation of COVID-19 and cardiovascular diseases is mediated through several key pathogenetic pathways. First, SARS-CoV-2 interacts with angiotensin-converting enzyme 2 (ACE2), which is expressed in myocardial cells, vascular endothelial cells, as well as in renal and pulmonary tissues. This receptor serves as the entry point for the virus into host cells, and its binding by SARS-CoV-2 disrupts the regulation of the renin-angiotensin-aldosterone system. This leads to vasoconstriction, sodium and water retention, the development of arterial hypertension, and structural remodeling of the left ventricular myocardium. Simultaneously, the cardioprotective effects of angiotensin-(1-7) are diminished, thereby exacerbating pre-existing ischemic heart disease, heart failure, and hypertension.

Second, endothelial dysfunction represents another crucial factor contributing to the severe course of this combined pathology. Following infection, SARS-CoV-2 induces injury to the endothelium, the inner lining of the vascular wall. This results in reduced production of vasodilators (particularly nitric oxide), increased vascular permeability, activation of procoagulant pathways, and enhanced thrombus formation. In patients with pre-existing cardiovascular disease, these mechanisms are already partially activated; therefore, viral injury significantly increases the risk of myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis.

Inflammation plays a central role in COVID-19-related cardiac damage. The cytokine storm accompanying severe infection induces systemic inflammation and myocardial injury. Elevated circulating levels of interleukins (IL-6, IL-1β), tumor necrosis factor-α (TNF-α), C-reactive protein, and ferritin are associated with the development of myocarditis. Myocarditis may be asymptomatic or manifest with arrhythmias, heart failure, chest pain, or cardiogenic shock. In some cases, acute myocardial injury develops in the absence of coronary obstruction, reflecting inflammation-induced or hypoxia-induced myocardial damage.

Hypoxia represents another plausible mechanism contributing to cardiovascular decompensation in COVID-19. In cases of severe pulmonary involvement (viral pneumonia, ARDS), arterial oxygen saturation decreases, thereby imposing additional

strain on the myocardium. In patients with pre-existing ischemic heart disease or myocardial hypertrophy, this may precipitate ischemia, impaired contractility, and the development of decompensated heart failure. Under hypoxic conditions, the increased demand for cardiac output cannot be adequately met, ultimately resulting in systemic circulatory dysfunction.

Another important mechanism underlying the complicated interplay between SARS-CoV-2 infection and cardiovascular disease is coagulopathy. SARS-CoV-2 activates the thrombotic cascade, manifested by elevated levels of D-dimer, fibrinogen, platelets, and other coagulation factors. This hypercoagulable state creates conditions for thrombotic complications, including myocardial infarction, embolic events, and disseminated intravascular coagulation (DIC). Given that patients with cardiovascular pathology already possess an elevated baseline risk of thromboembolic events, the probability of adverse and potentially fatal outcomes in this population is substantially increased.

A metabolic component is similarly significant: patients with cardiovascular disease frequently present with concomitant metabolic disorders (obesity, insulin resistance, dyslipidaemia), which further exacerbate the clinical course of COVID-19. Poor glycaemic control and excessive body weight are associated with intensified inflammation, worsening hypoxia, and structural-functional cardiac decompensation. Under these conditions, even a moderate severity of viral infection may rapidly progress to a severe, life-threatening state.

In patients with cardiovascular diseases, arrhythmias occur more frequently during COVID-19. This is attributed both to the direct involvement of the cardiac conduction system and to metabolic disturbances (hypokalaemia, acidosis), hypoxia, and the use of certain medications (e.g., antibiotics or antiviral agents capable of prolonging the QT interval). Atrial fibrillation, ventricular tachycardia, and extrasystoles are reported significantly more often in patients with COVID-19 who have pre-existing cardiac pathology.

Importantly, COVID-19 itself may serve as a potential trigger for the onset of new cardiovascular diseases. Cases of acute heart failure, myocarditis, pericarditis, Takotsubo syndrome, and type 2 myocardial infarction (secondary to hypoxia) have been documented in patients without prior cardiac conditions. Thus, SARS-CoV-2 infection may not only exacerbate existing cardiovascular disease but also precipitate its initial manifestation.

Therefore, the mutual aggravation of COVID-19 and cardiovascular pathology results from a combination of endothelial injury, hyperinflammation, impaired oxygenation, metabolic imbalance, and activation of thrombogenesis. Patients with cardiovascular disease are at significantly higher risk of severe COVID-19, complications, and mortality when infected with SARS-CoV-2.

Coronavirus disease COVID-19, caused by SARS-CoV-2, exerts a systemic impact on the human organism, and the hematopoietic system is among the most vulnerable. Patients infected with SARS-CoV-2 demonstrate a wide range of hematological alterations with substantial clinical and prognostic significance. The

principal underlying mechanisms include endothelial dysfunction, cytokine imbalance, hypercoagulation, disruptions in the hemostatic system, autoimmune reactions, and suppression of hematopoiesis. These factors act synergistically, giving rise to both direct cellular damage and indirect systemic complications.

One of the most common and clinically significant consequences of COVID-19 is the hypercoagulable syndrome, that is, an increased tendency toward excessive blood clotting. Many patients demonstrate elevated levels of D-dimer, fibrinogen, and prothrombin time – laboratory markers indicating activation of the coagulation cascade. Clinically, this manifests as deep vein thrombosis of the lower extremities, pulmonary embolism, ischemic stroke, or myocardial infarction. This condition, known as COVID-associated coagulopathy, is driven by the combined effects of virus-induced endothelial injury, platelet activation, the formation of neutrophil extracellular traps (NETs), and an intense inflammatory cytokine release, the so-called "cytokine storm." Endothelial damage caused by the virus via ACE2 receptor engagement creates a locally procoagulant state that promotes microthrombus formation.

Concurrently with hypercoagulation, a proportion of patients develop thrombocytopenia – a reduction in platelet count in peripheral blood. This phenomenon is explained by several mechanisms: direct inhibition of megakaryocytopoiesis in the bone marrow, increased platelet consumption during thrombus formation, sequestration of platelets in the spleen, and immune-mediated platelet destruction resembling immune thrombocytopenic purpura. The presence of thrombocytopenia correlates with disease severity and may serve as an early predictor of complications.

Another hallmark hematological feature of COVID-19 is lymphopenia – a reduction in lymphocyte count, particularly CD4+ T-helper cells and CD8+ cytotoxic T-cells. This may result from direct viral effects, cytokine-induced apoptosis, or impaired lymphocyte differentiation within the bone marrow. Lymphopenia is associated with impaired immune response, an increased risk of bacterial superinfections, and adverse prognosis: the lower the lymphocyte count, the higher the likelihood of severe disease. An elevated neutrophil-to-lymphocyte ratio (NLR), another typical finding, reflects systemic inflammation.

In some cases, patients with coronavirus infection may develop a severe complication – secondary hemophagocytic lymphohistiocytosis, which represents a form of hyperinflammatory syndrome. This condition is characterized by high fever, hepatosplenomegaly, cytopenia, hyperferritinemia, coagulation abnormalities, and multiorgan failure. Hematological involvement is mediated by massive activation of macrophages, which phagocytose blood cells and disrupt hematopoiesis. Additionally, such patients exhibit markedly elevated levels of inflammatory markers, including C-reactive protein, ferritin, interleukin-6, and D-dimer, which reflect the severity of the inflammatory response and serve as key parameters for monitoring the clinical course of the disease. It is also known that in patients with pre-existing chronic hematologic disorders (e.g., hemophilia, leukemia, anemias), COVID-19 may follow a substantially more severe course and be associated with an increased risk of complications.

In addition to coagulopathy and alterations in the leukocyte and platelet lineages, an important aspect of COVID-19-induced impairment of hematopoiesis is the development of anemia. Anemia in the context of coronavirus infection may be multifactorial and arise either during the acute phase of the disease or as a manifestation of post-COVID syndrome. The probable mechanisms of anemia in COVID-19 include both direct viral effects and secondary disturbances driven by immune, inflammatory, and metabolic responses to viral invasion. COVID-19 triggers the production of interleukin-6 (IL-6), which stimulates the synthesis of hepcidin, the principal regulator of iron metabolism. Hepcidin, in turn, inhibits ferroportin, the protein responsible for exporting iron from macrophages and enterocytes into the plasma, thereby leading to functional iron deficiency even in the presence of adequate total body iron stores. As a result, erythropoiesis becomes impaired, hemoglobin levels decline, and normocytic hypochromic anemia develops.

Another probable mechanism contributing to the development of anemia is the suppression of erythropoiesis in the bone marrow under the influence of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-1β, which inhibit the proliferation and differentiation of erythroid precursor cells. In some cases, SARS-CoV-2 may potentially infect hematopoietic progenitor cells directly or induce bone marrow hypoplasia. This is further exacerbated by hypoxia resulting from severe lung injury, which may alter the regulation of erythropoietin and lead to an imbalance in the stimulation of erythropoiesis. Elevated concentrations of inflammatory mediators also reduce the sensitivity of erythroid cells to erythropoietin, even when its production is increased.

In patients with coronavirus disease who are undergoing hemodialysis or prolonged oxygen therapy, hemolysis may develop due to mechanical injury to erythrocytes or oxidative stress induced by inflammation. In rare cases, the immune system may produce autoantibodies against erythrocytes in response to viral infection, leading to autoimmune hemolytic anemia. Finally, anemia in the post-COVID period is often associated with depletion of iron stores, vitamin B_{12}, or folic acid as a result of catabolic stress, reduced nutritional intake, malabsorption, or prolonged use of medications (e.g., antibiotics or antacids).

Thus, anemia in COVID-19 may arise from systemic inflammation, functional iron deficiency, impaired erythropoiesis, immune hemolysis, or hypoxia. Its presence complicates the course of the underlying disease, worsens tissue oxygenation, and reduces exercise tolerance, making its diagnosis and correction an essential component of management both in the acute and post-COVID phases.

Impact of COVID-19 on the hematopoietic system is profound, multifactorial, and clinically significant. It encompasses coagulation disturbances, hyperinflammatory syndromes, cytopenias, coagulopathies, and immune dysfunctions. These pathological alterations play a critical role in the development of severe forms of the disease and require timely identification and appropriate therapeutic intervention. Consequently, monitoring hematologic parameters, administering anticoagulants, implementing anti-

inflammatory therapy, and correcting immune dysregulation are integral components of contemporary clinical management of patients with COVID-19.

Analysis of the clinical course of COVID-19 demonstrates its polymorphic nature, which depends not only on the virulence of the SARS-CoV-2 strain but also on the individual characteristics of the host organism, immune status, and presence of comorbid conditions. Patients with an isolated course of the disease typically exhibit a more favorable prognosis, whereas individuals with concomitant pathology require close monitoring, early detection of complications, and active treatment with the involvement of a multidisciplinary team of specialists.

Consideration of the clinical features of COVID-19 depending on comorbid conditions is crucial for selecting an appropriate management strategy. This applies not only to pharmacological treatment but also to decisions regarding hospitalization, intensive care, rehabilitation, and long-term medical follow-up. Such an approach ultimately reduces mortality rates, improves the quality of medical care, and ensures effective utilization of healthcare resources in the context of the pandemic. Further detailed investigation of the impact of anemia on the course of COVID-19 is of paramount importance due to the multifactorial nature of this complication and its adverse effect on patients' clinical status. Anemia regardless of etiology reduces the oxygen-carrying capacity of blood, thereby exacerbating tissue hypoxia, which is frequently present in severe COVID-19. Evidence from the literature indicates that anemia is associated with increased mortality, higher rates of admission to intensive care units, and prolonged recovery times. Systemic inflammation induced by SARS-CoV-2 disrupts iron metabolism and suppresses erythropoiesis. Patients with pre-existing anemic conditions or risk factors for anemia warrant special attention, as COVID-19 may serve as a trigger for exacerbation or decompensation of these disorders. Currently, there is a limited number of large-scale studies systematically assessing the influence of anemia on both the acute phase of the disease and the development of post-COVID syndrome. Therefore, conducting prospective clinical studies aimed at elucidating the pathogenesis of anemia in COVID-19 and identifying optimal strategies for its monitoring and treatment remains an urgent scientific and clinical priority.

1.4. Community-acquired pneumonia associated with coronavirus disease: epidemiology, clinical features, comorbid conditions, complications, and specific aspects of patient management

Over the past five years, the global population has been exposed to the impact of coronavirus disease (COVID-19), caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which was identified through genome-sequencing technologies. The disease induced by SARS-CoV-2, designated COVID-19, continues to represent a significant medical and social challenge. Between 2019 and 2023, COVID-19 attained the status of a global pandemic. The severe and complicated course of the infection has continued to impose a substantial burden and socio-economic strain

on healthcare systems worldwide. To date, the pandemic has resulted in more than 7 million deaths. During this period, approximately 704.75 million individuals across the world have been infected.

According to data from the Ministry of Health of Ukraine (Public Health Center) and the National Security and Defense Council, as of 13 April 2024, a total of 5,557,995 SARS-CoV-2 infections had been confirmed in Ukraine (13.5% of the population), of which 112,418 cases were fatal (2.0%), while 5,445,577 individuals recovered (98.0%). At the peak of the epidemic, the overall mortality rate from COVID-19 reached approximately 2%, with 5-20% of patients requiring hospitalization, of whom 10-30% needed intensive care, thereby exerting substantial pressure on healthcare systems.

Among individuals with COVID-19, 35-40% develop mild pneumonia, 15-28% develop pneumonia of moderate severity, and 10-15% experience severe pneumonia requiring intensive care with respiratory support. In 5% of cases, the disease follows an extremely severe course, accompanied by complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, septic shock, pulmonary embolism, and multiple organ dysfunction (including injury to the kidneys, liver, and myocardium).

In May 2023, the World Health Organization (WHO) declared that COVID-19 was no longer a Public Health Emergency of International Concern, although the pandemic had not yet fully ended. WHO continues retrospective analyses aimed at updating epidemiological data on incidence and mortality. Globally, mortality from COVID-19-associated pneumonia remains high, exceeding 9.6% according to WHO data (reported in 29 countries).

SARS-CoV-2 belongs to the large family of RNA viruses Coronaviridae, which are capable of infecting both animals and humans. Based on serological and phylogenetic analyses, four genera are distinguished: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Prior to 2019, only six coronaviruses capable of infecting humans were known, four of which (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) typically cause mild upper respiratory tract infections (URTIs), although in certain cases they can induce severe URTI in children and the elderly. SARS-CoV and MERS-CoV, both of zoonotic origin, cause severe upper respiratory tract disease in human populations.

The novel coronavirus SARS-CoV-2 was first identified in December 2019 in Wuhan (China) during an outbreak of pneumonia of unknown etiology. This strain exhibits 99.8-99.9% nucleotide sequence homology with bat coronaviruses and demonstrates genetic similarity of approximately 50% with MERS-CoV and 80% with SARS-CoV. It encodes several structural proteins (the membrane protein, nucleocapsid protein, envelope protein, and spike glycoprotein) as well as a range of non-structural proteins. The spike protein consists of two subunits: S1, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor, and S2, which mediates membrane fusion. The virus initially infects epithelial cells of the nasopharynx, trachea, or olfactory mucosa, subsequently initiating the synthesis of replicase proteins and forming replication complexes.

Interferons induce an antiviral cellular state through the activation of interferon-stimulated genes, while cytokines activate B- and T-lymphocytes, facilitating viral clearance. If the virus is not neutralized at this stage, it disseminates into the lower respiratory tract, leading to alveolar involvement. In the lungs, SARS-CoV-2 predominantly infects type II alveolar cells, which produce surfactant essential for reducing surface tension within the alveoli.

SARS-CoV-2 can induce acute respiratory distress syndrome (ARDS), desquamation of the alveolar epithelium, edema, hemorrhage, and respiratory failure. A reduction in surfactant levels promotes alveolar collapse. As the infection progresses, impairment of gas exchange and escalating hypoxia occur, which may result in fatal outcomes. ARDS is characterized by inflammation, vascular injury, and loss of lung aeration. Patients with severe COVID-19 exhibit signs of systemic inflammation with elevated concentrations of cytokines including IL-1, IL-6, IL-8, IL-10, TNF-α, IFN-λ, IFN-β, CXCL-10, MCP-1, and MIP-1α. Activation of the immune response ultimately contributes to lung tissue injury.

Elevated levels of IL-6, IL-8, TNF, C-reactive protein, ferritin, and D-dimer at the time of hospital admission are predictors of a severe course of COVID-19. COVID-19 also causes gastrointestinal, cardiac, renal, and hepatic injury, as well as arrhythmias, coagulopathies, sepsis, and shock. The severity of COVID-19 is influenced by age, the presence of cardiovascular diseases, diabetes, obesity, and other risk factors. Recent studies have identified an association between the A1166C polymorphism of the AT1R gene and disease severity in the Ukrainian population. Carriers of the 1166C allele exhibit a higher frequency of severe disease and oxygen dependence.

The incubation period of COVID-19 typically ranges from 5 to 6 days, but may extend up to 14 days. Clinical manifestations vary from asymptomatic infection to severe disease with the development of ARDS and multiorgan failure. According to WHO data, the most common symptoms include fever (83-99%), cough (59-82%), fatigue (44-70%), dyspnea (31-40%), and myalgia (11-35%). Nonspecific symptoms include chest pain, nasal congestion, headache, diarrhea, nausea, vomiting, anosmia, and ageusia, which may precede respiratory symptoms, as well as possible neurological manifestations such as dizziness, agitation, and weakness.

Another study demonstrated the following clinical symptoms at disease onset: fever (83.7%), cough (81.4%), dyspnea (59.9%), and gastrointestinal disturbances (41.9%). COVID-19-associated pneumonia (NPS) may be asymptomatic in its early phase, meaning that the patient may not feel unwell while pulmonary inflammation progresses. COVID-19 leads to pulmonary surfactant deficiency, contributing to ARDS. Around days 5-7 from symptom onset, atypical pneumonia develops, typically multisegmental and rapidly progressing to confluent lobar involvement. Treatment duration also differs: 8-10 days of hospitalization in non-COVID community-acquired pneumonia versus approximately 15 days in NPS. Due to delayed symptom onset and clinical similarity to common respiratory infections, detection and management of COVID-19 pneumonia are challenging.

Pulmonary parenchymal inflammation is typically diagnosed on days 7-8 after symptom onset. Bilateral pneumonia is more common than unilateral disease (73.3% versus 26.7%). Patients with unilateral pneumonia have higher oxygen saturation (96% versus 94%, $p<0.001$). Significant differences between unilateral and bilateral cases were found in C-reactive protein levels (a 2.3-fold difference, $p<0.001$) and lymphocyte counts (a 1.4-fold difference, $p<0.001$). COVID-19 pneumonia is typically associated with dry cough; however, when bacterial superinfection develops, the cough becomes productive. Some studies report that up to 29% of patients with isolated viral pneumonia also presented with productive cough. The appearance of purulent sputum in a COVID-19 patient increases the likelihood of bacterial coinfection.

On physical examination, pulmonary findings in bacterial community-acquired pneumonia may vary and include dull or markedly diminished percussion notes, diminished and/or bronchial breath sounds, as well as focal, loud, fine crackles and/or crepitation. In viral CAP, objective pulmonary findings are usually minimal or absent, which is associated with the predominant involvement of the interstitial tissues of the lungs. At the same time, it is known that in bacterial pneumonias caused by M. pneumoniae, C. pneumoniae, and other atypical pathogens, physical examination of the lungs may likewise reveal no abnormalities. Thus, clinical signs alone do not allow for a reliable differentiation between viral and bacterial lung involvement in COVID-19-associated pneumonia.

Most patients with COVID-19 exhibit a normal leukocyte count, while one-third demonstrate leukopenia. Bacterial CAP is typically associated with leukocytosis above $10\text{-}12x10^9$/L and/or a left shift with more than 10% band forms. Pneumonias caused by atypical pathogens are generally characterized by the absence of leukocytosis. At the same time, leukopenia is also observed in bacterial pneumonias in immunocompromised patients and is considered a risk factor for adverse outcomes.

C-reactive protein (CRP) is a typical marker of inflammation and tissue injury. In viral pneumonias, particularly during the first days of illness, CRP levels may remain low, whereas in bacterial CAP they usually increase. However, CRP levels also rise during the immunopathological phase of COVID-19 (on days 5-7 of illness) and, therefore, CRP cannot serve as a reliable diagnostic marker of bacterial co-infection during this period. CRP concentration correlates with disease severity and prognosis in COVID-19. Nevertheless, because CRP is an acute-phase reactant that increases in all inflammatory conditions, including viral infections, its elevation should not be used as justification for initiating antibiotic therapy, as patients with COVID-19 may have high CRP levels in the absence of bacterial co-infection.

Studies have demonstrated that an increase in serum procalcitonin occurs under the influence of bacterial endotoxins and correlates with the severity of infection. In viral upper respiratory tract infections or non-bacterial inflammation, procalcitonin levels typically remain normal or only slightly elevated. Therefore, determining serum procalcitonin is useful for diagnosing bacterial co-infection in patients with COVID-19-associated pneumonia. A marked elevation of procalcitonin significantly increases the likelihood of bacterial superinfection and is considered the most specific biomarker.

However, it should be noted that some studies have shown elevated procalcitonin levels even in the absence of bacterial infection, particularly in patients with heart failure and renal dysfunction. Furthermore, an optimal lower threshold for procalcitonin concentration to reliably differentiate between bacterial and viral infection has not yet been established. Thus, procalcitonin, like any other diagnostic indicator, should be used to identify bacterial infection only in conjunction with other clinical criteria.

The diagnosis of pneumonia always requires the presence of localized infiltrative changes on chest radiography. In COVID-19-associated pneumonia, chest radiographs typically show multiple bilateral opacities with ill-defined and irregular margins, predominantly located in the basal and lateral subpleural regions. The diagnostic value of chest radiography increases as the disease progresses. Once the clinical picture becomes fully developed, radiography allows assessment of the location and extent of pneumonia; however, it is practically impossible to determine its etiology based on imaging alone.

Occasionally, bilateral infiltrative changes may be observed on radiographs in patients who have recovered from COVID-19. In the absence of clinical signs of active inflammation and with a recent history of pneumonia, such findings should be regarded as residual changes that require dynamic follow-up rather than antibiotic therapy. In COVID-19 pneumonia, delayed resolution of infiltrates or even paradoxical radiological progression despite clinical improvement is common. This may be misinterpreted as clinical deterioration, leading to unnecessary changes in antibiotic therapy. However, this pattern is now considered characteristic of organizing pneumonia, which is regarded as part of the normal reparative process of lung tissue.

Unfortunately, standard chest radiography has low sensitivity for detecting early abnormalities in COVID-19 and is therefore not suitable for early diagnosis of pulmonary involvement.

Chest CT has the highest sensitivity and specificity for detecting inflammatory changes in the lung parenchyma characteristic of COVID-19–associated pneumonia; its diagnostic accuracy reaches 93%. The typical CT findings in COVID-19 pneumonia include bilateral infiltrates in the form of ground-glass opacities (interstitial pattern) and areas of lung consolidation (alveolar pattern), predominantly located peripherally in the middle and lower lung zones. The ground-glass opacity pattern reflects reduced parenchymal aeration with preservation of the bronchovascular architecture. It is characteristic of viral injury and indicates interstitial involvement. However, this finding is nonspecific and may also be seen in other pneumonias or non-infectious disorders, such as idiopathic pulmonary fibrosis. Importantly, ground-glass opacities cannot be reliably detected on standard chest radiography. If a patient with confirmed COVID-19 has only ground-glass changes on CT, this indicates isolated viral involvement and does not justify antibiotic therapy.

Lung consolidation (alveolar infiltration) is more typical of bacterial pneumonia. Nonetheless, consolidation may also occur in COVID-19 in the absence of bacterial co-infection, reflecting progression of the viral process. Therefore, CT findings alone are not entirely specific and cannot determine the etiology of pneumonia without

considering the clinical and epidemiological context. As the evidence indicates, differentiating bacterial from viral pneumonia in COVID-19 is challenging. Current recommendations emphasize a comprehensive assessment of clinical presentation, laboratory parameters, and imaging findings.

Possible complications of COVID-19 include: reduced lung volume; pulmonary fibrosis that is often poorly responsive to treatment; cerebral ischemia; neurological manifestations (fatigue, dizziness, disorientation); secondary immunodeficiency; thrombosis; gastrointestinal dysfunction (including post-infectious irritable bowel syndrome); bronchitis; myocarditis; hepatic steatosis, among others. Complications associated with COVID-19 pneumonia include pulmonary embolism (observed only in bilateral pneumonia 5.6%) and increased mortality (2.2% in unilateral vs. 7.9% in bilateral pneumonia).

Antibiotic therapy in COVID-19 is appropriate only when reliable signs of bacterial co-infection are present. Such indicators include: transition from dry to productive cough with purulent sputum in a patient with confirmed COVID-19; a significant increase in procalcitonin levels; leukocytosis greater than 10-12x10^9/L and/or a left shift of more than 10%; or radiographic evidence of parenchymal consolidation on CT. Patients with severe COVID-19 requiring admission to the intensive care unit have a higher risk of bacterial co-infection; thus, empirical antibiotic therapy is justified in this group.

According to WHO recommendations, empirical antibacterial therapy may be administered to elderly patients, particularly those residing in long-term care facilities, and to children under five years of age. Absolute indications for prescribing antibiotics in COVID-19-associated pneumonia include only confirmed bacterial infection, that is, a positive microbiological culture of sputum or blood. However, numerous barriers limit the implementation of this approach in clinical practice. For instance, sputum cultures yield positive results in no more than 30-50% of cases. Distinguishing etiologically significant pathogens from commensal flora of the nasopharynx in sputum samples is often challenging. Moreover, obtaining results from microbiological cultures requires 3-5 days. Consequently, in real-world clinical settings, antibacterial therapy is initiated empirically in most cases.

Empirical therapy for community-acquired bacterial pneumonia is selected based on the most likely pathogens, taking into account disease severity, comorbid conditions, and the risk of resistant microorganisms. The most common pathogens in influenza-associated bacterial pneumonia include S. pneumoniae, S. pyogenes, S. aureus, H. influenzae, and M. catarrhalis. According to CDC data, pregnant women infected with influenza A (H1N1) in 2009 had a high risk of secondary CABP caused by Klebsiella spp., associated with poor clinical outcomes and high mortality (up to 30%). In patients receiving mechanical ventilation, there is a risk of ventilator-associated pneumonia, which during the last influenza pandemic was most commonly caused by Acinetobacter baumannii, Achromobacter xylosoxidans, and methicillin-resistant S. aureus (MRSA).

Current evidence regarding the most frequent bacterial co-infections in COVID-19 remains limited and inconsistent. Several studies identified Streptococcus

pneumoniae, Haemophilus influenzae, Staphylococcus aureus, and Klebsiella pneumoniae as the most common co-infecting pathogens. Chong WH et al. (2021) conducted a review of culture-confirmed secondary bacterial and fungal pneumonias developing within 48 hours after hospital admission in patients with COVID-19. A meta-analysis of 14 studies reported a 16% prevalence of secondary bacterial infections among hospitalized patients, ranging from 4.8% to 42.8%. The prevalence of secondary fungal infections was 6.3%, with a range of 0.9-33.3%, based on 18 observational studies. Most patients who developed secondary bacterial or fungal pneumonia had severe COVID-19 requiring mechanical ventilation and intensive care.

According to 24 observational studies, bacterial pathogens most frequently isolated from upper respiratory tract cultures in patients with COVID-19 pneumonia included: Pseudomonas aeruginosa (21.1%), Klebsiella spp. (17.2%), Staphylococcus aureus (13.5%), Escherichia coli (10.4%), and Stenotrophomonas maltophilia (3.1%). Fungal pathogens were predominantly represented by Aspergillus species; across studies, the most frequently detected were A. fumigatus, A. flavus, A. calidoustus, A. citrinoterreus, A. niger, A. terreus, and A. versicolor. One observational study also identified Mucor species and Fusarium proliferatum in upper respiratory tract cultures of patients with severe COVID-19 pneumonia.

Average time to diagnosis of secondary bacterial and fungal infections from the moment of hospitalization was 10 days (range: 2-21) and 9 days (range: 4-18), respectively. Empirical therapy was administered in 60-100% of cases. Most observational studies did not report data on antimicrobial resistance of the identified pathogens; however, several publications described the detection of critical multidrug-resistant microorganisms in respiratory and blood cultures of critically ill patients with COVID-19, including extended-spectrum β-lactamase (ESBL)-producing Klebsiella pneumoniae; ESBL Escherichia coli; multidrug-resistant Pseudomonas aeruginosa; carbapenem-resistant K. pneumoniae; as well as methicillin-resistant Staphylococcus aureus (MRSA).

The pooled prevalence of co-infections was 19% (95% CI: 14-25%), and that of superinfections was 24% (95% CI: 19-30%). The distribution by pathogen type was as follows: viral co-infections – 10% (95% CI: 6-14%), viral superinfections – 4% (95% CI: 0-10%), bacterial co-infections – 8% (95% CI: 5-11%), bacterial superinfections – 20% (95% CI: 13-28%), fungal co-infections – 4% (95% CI: 2-7%), and fungal superinfections – 8% (95% CI: 4-13%).

Other studies have reported specific microorganisms associated with co- and superinfections in patients with COVID-19. The three most common bacteria identified among co-infected patients were K. pneumoniae (9.9%), Streptococcus pneumoniae (8.2%), and S. aureus (7.7%). The most frequently isolated fungi causing co-infections belonged to the genus Aspergillus. Among patients with superinfections, the predominant bacteria were Acinetobacter spp. (22.0%), Pseudomonas spp. (10.8%), and E. coli (6.9%), while fungi of the genus Candida accounted for 18.8%.

When bacterial superinfection occurs in patients with moderate, severe, or critical community-acquired pneumonia associated with COVID-19, antibacterial therapy is

administered according to existing national guidelines. In Ukraine, empirical antibiotic therapy for pneumonia is regulated by the Adapted Clinical Guideline approved by the National Academy of Medical Sciences in 2019. According to these recommendations, for hospitalized patients, first-line therapy consists of a combination of β-lactam antibiotics (aminopenicillins, preferably β-lactamase inhibitor-protected formulations, or third-generation cephalosporins such as ceftriaxone or cefotaxime) with macrolides (azithromycin, clarithromycin).

Alternative regimens include respiratory fluoroquinolones (levofloxacin, moxifloxacin), administered either as monotherapy or in combination with β-lactam antibiotics. The duration of antibacterial treatment for pneumonia is generally at least 7 days. Recent studies suggest that shorter courses may be appropriate when clear clinical improvement is achieved with initial therapy.

Comorbidities in the stage of decompensation, such as decompensated diabetes mellitus, severe chronic respiratory disease, severe chronic cardiovascular disease, immunosuppressive states, and renal failure, must also be considered, as they significantly increase the risk of poor outcomes. Additional comorbid conditions that may worsen prognosis include complicated diverticulitis, pyoderma, and inadequate response to immunosuppressive therapy.

According to the 2022 WHO recommendations, COVID-19 severity is classified as follows:

• Non-severe: absence of signs of severe or critical disease.

• Severe: $SpO_2<90\%$, radiological or clinical evidence of pneumonia and/or signs of severe ARDS.

• Critical: presence of ARDS, sepsis, or septic shock.

According to the latest Ukrainian clinical guideline (2022), the severity of COVID-19 illness is classified as follows: mild disease – no defined signs of viral pneumonia or hypoxia; moderate disease – clinical manifestations of pneumonia (dyspnea, fever, cough) are present, but there are no signs of severe pneumonia, including $SpO_2\geq90\%$ in the air; severe COVID-19 is characterized by evidence of lung inflammation accompanied by a respiratory rate > 30 breaths/min, severe ARDS, and/or $SpO_2<90\%$. In addition, according to the most recent clinical protocol, pathological conditions consistent with the WHO classification are distinguished. Approximately 80% of infected patients exhibit involvement limited to the upper and conducting airways. However, in nearly 20% of cases, COVID-19 progresses to the gas-exchange regions of the lungs, leading to hypoxia and pneumonia with a ground-glass opacity pattern.

According to WHO recommendations, the primary diagnostic algorithm for a patient with acute respiratory infection who has had contact with a confirmed or probable COVID-19 case is timely PCR testing. For symptomatic patients with a high clinical suspicion of pneumonia, if PCR testing is unavailable or results are delayed, chest radiography is recommended. To diagnose COVID-19 and its complications, in addition to lung radiography, computed tomography of the lungs and ultrasonography of the lungs and pleural cavities may be performed. Laboratory diagnostics include a

complete blood count and C-reactive protein assessment. In severe disease, mandatory laboratory tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), D-dimer (>1 μg/mL), troponins T and I, and serum ferritin.

Management of pneumonia in case of COVID-19 should be guided by disease severity and risk of deterioration, taking into account the patient's comorbidities, home environment, and social support. Most patients with mild disease (symptomatic without pneumonia or hypoxia, or asymptomatic/presymptomatic individuals with a positive SARS-CoV-2 PCR test) do not require emergency intervention or hospitalization. Home-based self-care may be appropriate, including maintaining adequate hydration and using simple analgesics and antipyretics. WHO guidelines emphasize that patients and household members should remain in home isolation for at least 10 days after symptom onset (or after a positive COVID-19 test in asymptomatic individuals), plus an additional three days without fever and respiratory symptoms.

Antibiotic selection is indicated in moderate or severe pneumonia. According to Langford B.J. et al., both bacterial co-infection at presentation and secondary bacterial infection after presentation are relatively uncommon in patients with COVID-19-associated pneumonia. Nevertheless, three-quarters (74.6%) of hospitalized COVID-19 patients receive antibiotics. WHO data indicate that antibiotic therapy in moderate disease is justified when a clinical diagnosis of pneumonia or sepsis is established, when individual risk of bacterial co-infection is high, and in elderly patients. Clinical and laboratory findings must be considered, including complete blood count, procalcitonin, and bacteriological testing.

According to the latest Ukrainian clinical guideline, in moderate or severe pneumonia, amoxicillin/clavulanate in combination with macrolides is the preferred regimen. Second- and third-generation cephalosporins and respiratory fluoroquinolones may also be used.

Patients with respiratory failure should be provided with supplemental oxygen therapy. According to the recommendations of NHS England, it is advised to maintain SpO_2 within the range of 92-96% (or 88-92% in patients with known hypercapnic respiratory failure or at risk of developing hypercapnic respiratory failure). In accordance with the current Ukrainian clinical guideline, adults presenting with life-threatening symptoms require immediate measures to restore upper airway patency and initiation of oxygen therapy to achieve a target $SpO_2 \geq 94\%$. The appropriate oxygen flow rate may be delivered using a nasal cannula (up to 5 L/min), a Venturi mask (6-10 L/min), or a non-rebreather mask (10-15 L/min). WHO recommendations also allow the use of monoclonal antibodies in patients with uncomplicated pneumonia who are at increased risk of hospitalization, including unvaccinated individuals, patients over 60 years of age, and/or those with comorbidities.

Findings reported by Horby P. and colleagues demonstrated that administration of dexamethasone 6 mg once daily for 10 days (versus standard care) reduced 28-day all-cause mortality among patients receiving invasive mechanical ventilation (29.3% vs.

41.4%) or supplemental oxygen alone (23.3% vs. 26.2%), whereas no benefit was observed in patients who did not require supplemental oxygen.

The literature describes studies assessing the efficacy of remdesivir in COVID-19. Remdesivir is an adenosine nucleotide analogue that undergoes intracellular metabolism to its active triphosphate form. In this active form, it inhibits viral replication by binding to the RNA-dependent RNA polymerase of the virus. It has previously demonstrated in vitro activity against SARS-CoV and MERS-CoV, and recent in vitro findings confirm its activity against SARS-CoV-2. However, no study has yet shown substantial clinical benefit or a significant effect on survival among patients.

Positive experimental data have been obtained regarding the use of the IL-6 receptor inhibitor tocilizumab, as well as the potential efficacy of antihypoxants, such as ethylmethylhydroxypyridine succinate. Nevertheless, convincing clinical evidence supporting their routine use in COVID-19 remains insufficient.

Thus, the epidemiology, age-related, gender-specific, and clinical features of the course of pneumonia associated with COVID-19, as well as the structure of comorbidities, remain insufficiently studied, which underscores the need for further research in this area.

1.5. Pathomorphological changes in COVID-19-associated community-acquired pneumonia and comorbid conditions

The study of pathomorphological alterations in COVID-19 is essential for understanding the pathogenesis, clinical course, and outcomes of lung involvement, which remains the leading cause of mortality in this infection. While clinical, laboratory, and instrumental diagnostic methods enable assessment of the degree of respiratory failure and inflammatory activity, it is morphological examination of tissues that provides objective confirmation of the structural and cellular disturbances occurring at the level of alveoli, capillaries, and interalveolar septa.

Pathomorphological examinations of the lungs in SARS-CoV-2 infection enable a detailed description of the sequence of lesions – from acute diffuse alveolar damage to the development of organizing pneumonitis, microthrombosis, and fibrosis. The analysis of these changes facilitates the identification of specific morphological markers of COVID-19 that may distinguish it from other viral or bacterial pneumonias and explains the resistance of certain clinical forms to standard therapy.

The rationale for conducting pathomorphological studies lies not only in diagnostic verification, but also in determining the cause of death, assessing treatment efficacy, analyzing complications (thromboembolic, hemorrhagic, interstitial), and elucidating the mechanisms underlying the progression of respiratory distress syndrome. Morphological data also hold significant scientific value in shaping pathogenetic models that help interpret clinical and radiological manifestations and optimize therapeutic approaches, particularly regarding the use of anticoagulants,

corticosteroids, and antifibrotic agents. Incorporating pathomorphological examination of autopsy material into the framework of comprehensive COVID-19 research is a justified and necessary step toward achieving a systematic understanding of the morphogenesis of lung injury, identifying predictors of adverse disease progression, and developing more effective methods of prevention and treatment of respiratory system involvement in coronavirus disease.

The pathomorphological picture of lung injury in COVID-19 is remarkably multifaceted, reflecting complex interactions among viral invasion, immune response, endothelial injury, and microcirculatory disturbances. Histological analyses demonstrate that the principal morphological substrate is diffuse alveolar damage, which morphologically correlates with the clinical acute respiratory distress syndrome. In most cases, it presents as a mixed pattern, characterized by the simultaneous presence of acute, proliferative, and fibrotic phases within a single lung tissue specimen, indicating a wave-like, recurrent course of the pathological process.

In the initial stages of the infectious process, acute serous-exudative changes predominate. The alveolar spaces are filled with proteinaceous exudate containing numerous erythrocytes, desquamated alveolocytes, neutrophils, macrophages, and plasma cells. In many areas, the formation of hyaline membranes is noted, which results from the coagulation of plasma proteins and fibrin deposited on the damaged alveolar epithelium. The hyaline membranes form continuous eosinophilic bands that markedly reduce gas exchange and contribute to the development of severe hypoxia.

The interalveolar septa are edematous, engorged with blood, and infiltrated with mononuclear cells. The endothelial cells of the capillaries are hypertrophied, dystrophically altered, and in some places detached from the basement membrane. Microthrombi are frequently detected within the lumens of capillaries and small arterioles, representing a morphological manifestation of coronavirus-induced endotheliopathy and a hypercoagulable syndrome. In the pulmonary venules and arterioles, foci of fibrinoid necrosis of the vascular wall are observed, around which perivascular lymphocytic infiltrates are formed. Against the background of these changes, areas of massive hemorrhage are often encountered, which may coalesce to form foci of pulmonary hemorrhagic infarction. Such lesions exacerbate respiratory failure and increase the risk of secondary bacterial infections.

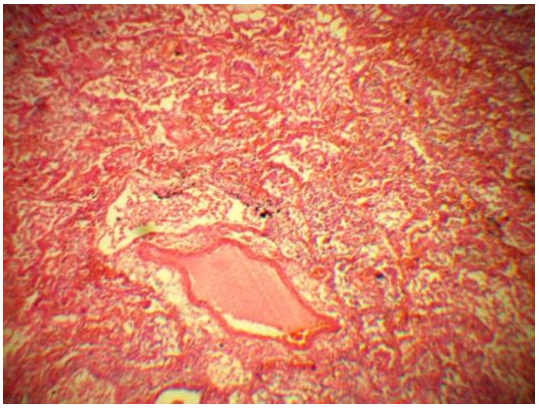
After 7-10 days from the onset of the disease, regenerative-proliferative changes predominate in the lung tissue. Type II alveolocytes actively proliferate, forming multilayered areas in which the cells exhibit enlarged hyperchromatic nuclei, polygonal morphology, and abundant cytoplasm with numerous vacuoles. Multinucleated syncytia are frequently observed, resulting from the fusion of damaged cells, reflecting the cytopathic effect of SARS-CoV-2.

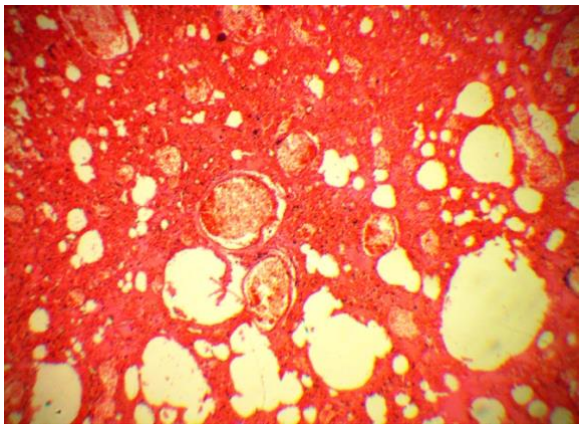
In the alveolar lumens, instead of exudate, granulation tissues appear, containing fibroblasts, myofibroblasts, collagen fibers, and newly formed vessels. These structures represent the morphological manifestation of the organization of inflammatory exudate, which may subsequently transform into fibrous tissue. The interalveolar septa are

thickened, with signs of fibroelastosis, and are rich in plasma cells, macrophages, CD3+ lymphocytes, and CD68+ histiocytes.

A characteristic feature of COVID-19 is the high activity of endothelial cells, which participate in neoangiogenesis, forming new, chaotically arranged vessels. This process represents an attempt to compensate for hypoxia, while simultaneously leading to structural remodeling of the microcirculatory bed.

At the late stages (3-6 weeks from disease onset), pulmonary parenchymal fibrosis develops in a subset of patients. The alveolar structures are replaced by dense connective tissue, altering the lung architecture. Areas of "honeycombing," characteristic of post-COVID interstitial fibrosis, form within pulmonary lobules. A significant proportion of capillaries is obliterated, with fibrin deposition, hyalinosis, and fibrinoid necrosis present in the vascular walls. In some specimens, secondary pulmonary hypertension and hypertrophy of the arteriolar wall are identified, reflecting compensatory responses to chronic hypoxia.





Figures 1.5.1, 1.5.2. Marked congestion, impaired rheological properties of blood in the examined tissues, and focal hemorrhages in the lung tissue

The mucous membrane of the bronchial tree is characterized by pronounced active metaplastic and dystrophic processes. The columnar ciliated epithelium undergoes squamous metaplasia; hyperplasia of goblet cells is observed, leading to excessive mucus production. Mucous plugs accumulate in the bronchiolar lumens, obstructing drainage and promoting the development of atelectasis. The subepithelial layer is infiltrated with lymphocytes, plasma cells, macrophages, and occasionally eosinophils. In severe cases, destruction of the ciliated epithelium is documented, with its detachment in sheets and the formation of erosions. Such alterations markedly impair mucociliary clearance, decrease the barrier function of the mucous membrane, promote secondary bacterial or fungal colonization, and slow reparative processes.

Dense lymphoid aggregates are detected in the lung parenchyma around vessels and bronchi, consisting predominantly of CD8+ cytotoxic lymphocytes, macrophages, and plasma cells. In certain areas, giant multinucleated cells with viral inclusions are identified, representing direct morphological evidence of viral epithelial injury.

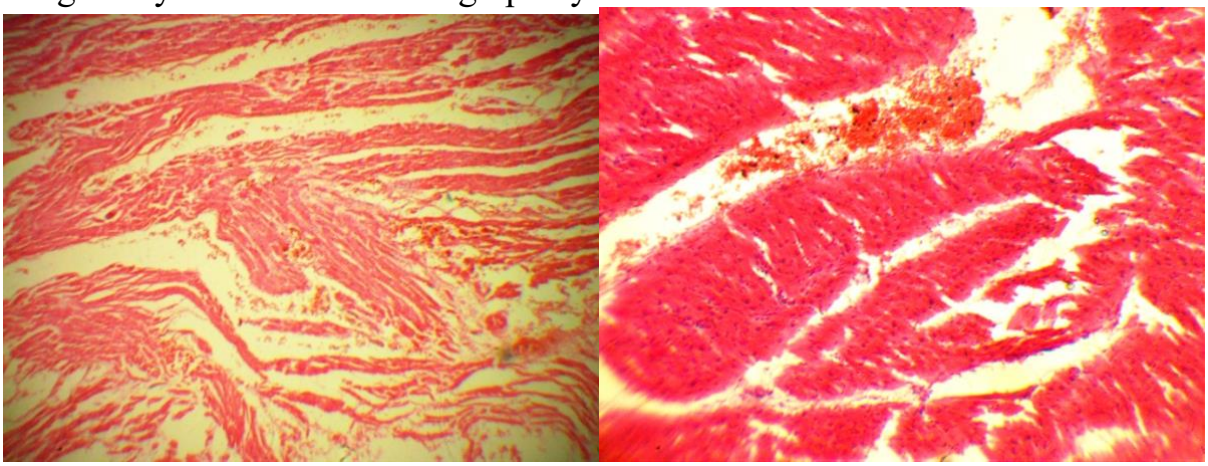
Immunohistochemical studies confirm the presence of viral antigen in alveolocytes, macrophages, and endothelial cells, indicating the systemic nature of the involvement. The presence of interstitial infiltrates with a predominance of CD4+ lymphocytes and macrophages indicates a chronic phase of inflammation, which may persist even after clinical recovery. These residual changes explain the prolonged post-COVID syndrome with persistent dyspnea, cough, and reduced oxygen saturation.

Thus, the pathomorphological changes in the lungs in COVID-19 represent a complex combination of acute inflammation, endothelial dysfunction, microthrombosis, epithelial proliferation, and fibrosis. These processes are interrelated and determine the severity of the clinical course, the duration of hypoxia, and the likelihood of developing irreversible alterations of the pulmonary parenchyma. Pathomorphological examination remains the only method that allows complete reconstruction of the morphogenesis of lesions, assessment of treatment effectiveness, and the formation of scientifically grounded strategies for the prevention of post-COVID complications.

Pathomorphological examination in patients with coronavirus disease has gained particular significance in the context of comorbid pathology, as it is the combination of viral injury with pre-existing chronic diseases that determines the polymorphism of clinical manifestations, the complexity of diagnosis, the variability of morphological changes, and ultimately the prognosis of disease progression. Conducting a comprehensive pathomorphological study not only enables verification of the cause of death or severe complications, but also deepens the understanding of the pathogenetic mechanisms of mutual aggravation of COVID-19 with somatic diseases of various organs and systems.

In patients with cardiovascular diseases (ischemic heart disease, arterial hypertension, chronic heart failure), the morphological features of cardiac and vascular involvement in COVID-19 are pronounced and complex, which contributes to a severe or fatal disease course. The SARS-CoV-2 virus affects endothelial cells via ACE2 receptors, which are widely expressed on the endothelium of arterioles, venules, and capillaries, leading to the development of systemic endotheliopathy. Morphologically, this is manifested by dystrophy, edema, and desquamation of endothelial cells; the vascular lumen often contains platelet aggregates, fibrin strands, and microthrombi, confirming a hypercoagulable syndrome. In the myocardium, foci of ischemic necrosis of cardiomyocytes are observed, along with intercellular edema and infiltration of the interstitium by lymphocytes and macrophages, indicating a combination of hypoxic and inflammatory injury. Particular attention is drawn to pronounced congestion of capillaries and venules, accompanied by stasis and erythrocyte sludging, which morphologically reflects microcirculatory disturbances in hypoxia. In the setting of arterial hypertension or atherosclerosis, intimal thickening, hyperplasia of vascular smooth muscle cells, focal fibrin deposition, and occasionally fibrinoid necrosis of small arteries are noted. In perivascular areas, lymphoplasmacytic infiltration is recorded, indicating an immuno-inflammatory component of injury. Such morphological changes form the substrate of systemic hypoxia, which exacerbates the damaging effects of COVID-19 on the myocardium.

Additional signs of cardiomyocytic dystrophy are identified in the myocardium, including vacuolization of the sarcoplasm, nuclear hyperchromasia, fragmentation of myofibrils, and in severe cases areas of coagulative necrosis. In a subset of patients, signs of myocarditis are observed, with a predominance of CD68+ macrophages and T lymphocytes, indicating a virus-induced immune response. The morphological cardiac changes are often combined with vascular injury in other organs (lungs, kidneys, brain), confirming the systemic nature of angiopathy in COVID-19.



Figures 5.1.3, 5.1.4. Marked congestion of the venous-capillary bed, uneven blood filling of the arteries, erythrostasis, microthrombi in the capillaries, pronounced diapedeses haemorrhages, and thickened walls of intramural arteries due to myocardial tissue sclerosis

Patients with type 2 diabetes mellitus represent one of the most vulnerable groups in SARS-CoV-2 infection, and pathomorphological studies demonstrate profound systemic alterations that extend far beyond classical pulmonary involvement. Chronic hyperglycemia, insulin resistance, and oxidative stress create a favorable environment for the development of endothelial dysfunction, microangiopathies, and hypercoagulable disturbances, which markedly aggravate the severity of COVID-19. In the pulmonary tissue of such patients, massive microthrombosis of capillaries and venules, hyalinosis of vascular walls, pronounced congestion of interalveolar septa, focal hemorrhages, and necrotizing vasculitis accompanied by diffuse alveolar damage are typically observed. Compared with patients without diabetes mellitus, injury to type II alveolocytes is deeper in such individuals, with pronounced cellular atypia, nuclear hypertrophy, and hypersecretion of surfactant, which leads to impaired gas exchange and the development of acute respiratory distress syndrome.

In the microcirculatory bed, signs of a hypercoagulable syndrome are documented, including fibrin deposition, microthrombosis in arterioles and venules, and erythrocyte sludging, which morphologically reflects decompensation of systemic hemocirculation. Histochemically, increased expression of platelet activation markers (CD61, vWF) and markers of oxidative stress is detected, indicating endothelial injury caused by reactive oxygen species. This supports the hypothesis that hyperglycemia stimulates glycation of endothelial proteins, reducing their anticoagulant properties and enhancing the prothrombotic potential. Simultaneously, in the liver of such patients,

signs of hepatocellular dystrophy, cytoplasmic vacuolization, disruption of the trabecular architecture, microthrombosis of portal tracts, and sinusoidal stasis are observed, indicating a combination of hypoxic, toxic, and inflammatory injury. Electron microscopy reveals dilation of the endoplasmic reticulum, mitochondrial destruction, and glycogen accumulation – features characteristic of decompensation of various metabolic pathways.

In the kidneys of patients with COVID-19 and concomitant type 2 diabetes mellitus, typical manifestations of glomerular microangiopathy are documented, including thickening of the basement membranes, glycosylation-related endothelial injury, narrowing of capillary loops, hyalinosis of afferent arterioles, and focal glomerulosclerosis. Degenerative changes of podocytes and foci of tubulointerstitial inflammation are frequently observed, confirming the systemic nature of the injury. The presence of these alterations explains the high incidence of acute kidney injury in patients with COVID-19 and comorbid type 2 diabetes mellitus.

Morphologically, these findings confirm the pathogenetic concept according to which hyperglycemia and insulin resistance amplify the cytokine response and endothelial activation, causing excessive production of IL-6, TNF-α, C-reactive protein, hepcidin, and stimulating fibrogenesis in the pulmonary parenchyma. This forms the phenomenon of the “cytokine storm,” which aggravates the inflammatory process and promotes fibrotic transformation of the lung tissue.

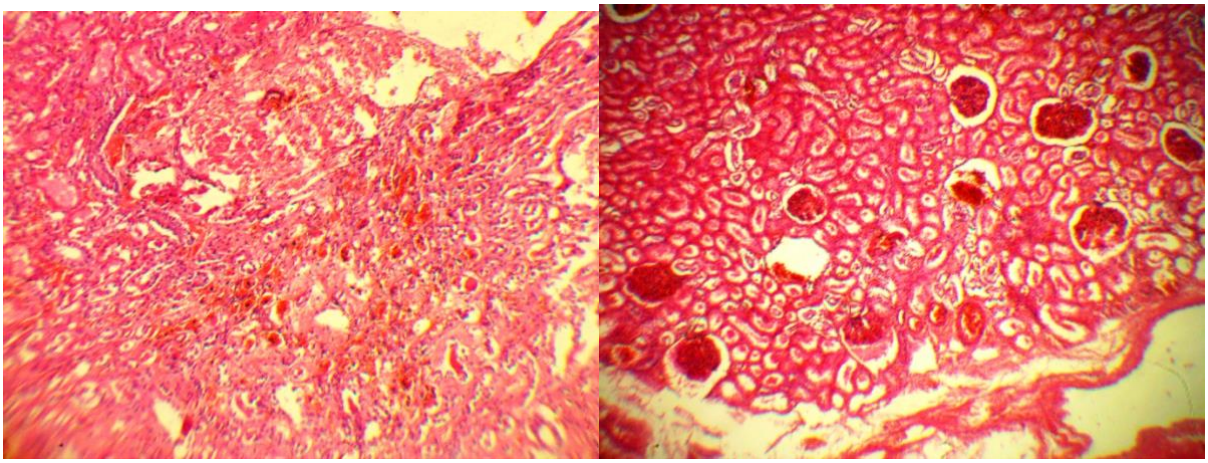


Figure 1.5.5, 1.5.6. Marked congestion of the interstitial vessels, glomerular and tubular capillaries, pronounced diapedesis hemorrhages, swollen vascular wall fibers, and mildly thickened arterial walls due to renal tissue sclerosis

In patients with obesity and metabolic syndrome, the pathomorphological changes in COVID-19 exhibit the nature of a systemic metabolic-inflammatory injury that affects not only the pulmonary parenchyma but also other organs and systems. Excess adipose tissue in this context acts not as a passive energy depot but as a metabolically active endocrine organ producing a wide spectrum of adipokines (leptin, resistin, visfatin, adiponectin) and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, etc.). These molecules initiate a cascade of chronic low-grade inflammation, which,

when combined with the cytokine storm in COVID-19, results in excessive immune activation, endothelial dysfunction, and thrombosis of small vessels.

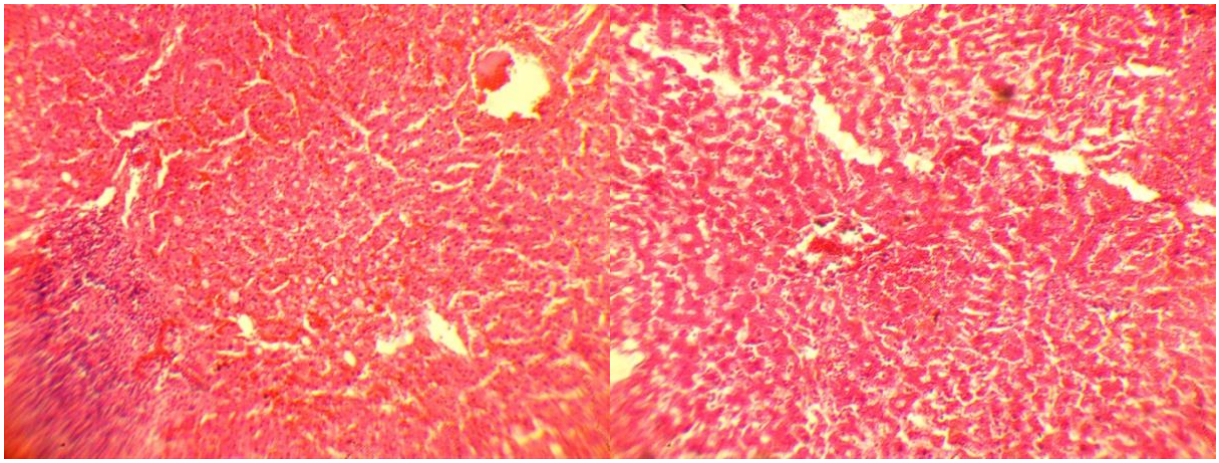
Morphologically, in the lungs of such patients, massive interstitial edema, thickening of interalveolar septa, and pronounced cellular infiltration, primarily represented by CD68+ macrophages, CD3+ lymphocytes, plasma cells, and neutrophils, are observed. Foci of fat embolism are frequently identified, arising as a consequence of endothelial damage and the entry of lipid droplets into the bloodstream. The alveolar spaces are filled with proteinaceous exudate, cellular detritus, and fragments of hyaline membranes, indicating progression into the fibrotic phase of diffuse alveolar damage. Concurrently, signs of diffuse or focal fibrosis are documented, morphologically manifested by fibroblast proliferation, deposition of collagen fibers, and hyperplasia of type II alveolocytes, which represents a compensatory response to chronic hypoxia. In the endothelial cells of vessels, cytoplasmic vacuolization, mitochondrial destruction, overexpression of hypoxia markers (HIF-1α), and neoangiogenesis – the formation of new, structurally altered capillaries – are detected. This pathological neoangiogenesis reflects an attempt of tissues to compensate for prolonged hypoxia, while simultaneously contributing to further remodeling of the vascular bed.

Particularly important is the identification of activation of adipokine-dependent signaling pathways, including NF-κB and JAK/STAT, which induce cytokine synthesis and inhibit apoptosis of inflammatory cells. This mechanism establishes a persistent chronic inflammatory background that remains even after viral elimination. The pathomorphological features of this process include an increased number of CD68+ macrophages, hyperplasia of smooth muscle cells within vascular walls, infiltration of the adventitia by lymphocytes, and thickening of the basement membranes of the alveolar epithelium. Additionally, in the adipose tissue of patients with COVID-19 and obesity, pronounced dystrophy of adipocytes, reduction of their size, signs of apoptosis, and activation of resident macrophages (M1 phenotype), which release large quantities of pro-inflammatory mediators, are observed. This leads to the further release of free fatty acids, which act as lipotoxins, promoting oxidative stress and inflammation.

Thus, the pathomorphological picture in patients with obesity and metabolic syndrome in COVID-19 reflects a synergy of metabolic inflammation, vascular injury, and hypoxia, leading to progressive fibrosis of the lung tissue and systemic endothelial damage. These data confirm that obesity is not only a risk factor for severe COVID-19 but also a morphologically verified multiorgan syndrome that sustains systemic inflammation even after the resolution of the acute phase of the infection.

In patients with chronic liver diseases including alcoholic, metabolic-associated or non-alcoholic steatohepatitis, viral hepatitis, autoimmune processes, and liver cirrhosis, pathomorphological examination has exceptionally important diagnostic and prognostic value in SARS-CoV-2 infection. The virus is capable of infecting hepatocytes and cholangiocytes via ACE2 and TMPRSS2 receptors, which are expressed in the cells of the bile ducts and the vascular endothelium of the liver. As a result, the injury has a combined character – a combination of direct virus-induced cytopathic effects, systemic hypoxia, endothelial dysfunction, and immune-

inflammatory damage. Microscopically, in such patients, hepatocellular dystrophy of various types is observed, predominantly granular, hydropic, or vacuolar, with pericentral and mosaic distribution. These changes reflect a decrease in cellular energy potential and impairment of membrane transport. In certain areas, focal necroses of hepatocytes, either coagulative or apoptotic types of cell death, are detected, as well as microthromboses in the vessels of the portal tracts and sinusoids, indicating a hypercoagulable state and hypoxic injury of hepatic tissue. Congestion of central veins, sinusoidal blood stasis, dilation of the perisinusoidal spaces of Disse, and the presence of microhemorrhages are frequently observed, morphologically corresponding to the syndrome of congestive or ischemic hepatitis.



Figures 1.5.7, 1.5.8. The vessels of the portal tracts and central veins are markedly congested, with signs of blood separation; sinusoidal capillaries show focal engorgement, and pronounced diapedesis haemorrhages are present within the liver tissue

In patients with metabolic-associated steatohepatitis, fat inclusions in the cytoplasm of hepatocytes (predominantly of the macrovesicular type), ballooning degeneration of cells, pericellular fibrosis, and activation of Ito cells (hepatic stellate cells) are identified, indicating active fibrogenic processes. In combination with COVID-19, such changes progress: foci of necrosis appear around central veins, interstitial inflammatory infiltrates develop, and necrotizing endotheliitis in small vessels is observed, pointing to the intensification of cytokine-mediated inflammation. In patients with severe forms of the disease, massive activation of CD68+ macrophages and pronounced expression of IL-6, TNF-α, and C-reactive protein in hepatocytes are seen, morphologically confirming the phenomenon of the “cytokine storm”

In patients with alcoholic liver injury, the morphological picture is further characterized by the presence of Mallory bodies, degenerative-type mitoses, pronounced pericellular fibrosis, and hyperplasia of Kupffer cells. Under the influence of COVID-19, these changes are aggravated by multiple foci of necrosis, inflammatory cuffs around the portal tracts, and microthromboses of small veins, indicating exacerbation of alcoholic steatohepatitis and activation of fibrogenic processes.

In patients with liver cirrhosis in the context of COVID-19, portal-central fibrous septa, regenerative nodules of varying size, dilation of central veins, and congestive engorgement are observed. In some specimens, plasmacytic infiltration, foci of cholangitis, microabscesses in the periportal zones, and vascular hyalinosis are documented, indicating decompensation of the underlying pathology and activation of autoimmune-inflammatory processes.

Pathomorphological examination in such cases is indispensable, as it allows differentiation between direct virus-induced hepatocytic injury and drug-induced hepatotoxicity, hypoxic hepatitis, or exacerbation of chronic hepatitis of another etiology. Morphological criteria – the type and localization of necrosis, the presence of thromboses, the degree of steatosis, fibrosis, and inflammatory infiltration – often have decisive clinical significance for determining further treatment strategy, including the choice of antiviral, hepatoprotective, or anticoagulant therapy.

In patients with chronic and diabetic kidney disease, the course of COVID-19 is accompanied by profound pathomorphological alterations that reflect a combination of direct viral cytopathic effects, systemic endothelial injury, hypoxia, and chronic metabolic stress. Such lesions lead to rapid deterioration of renal filtration capacity, development of acute kidney injury, and formation of multiorgan dysfunction.

Microscopically, pronounced glomeruloendotheliopathy is identified, manifested by endothelial cell swelling, narrowing of capillary loops, microthromboses, erythrocyte sludging, and fibrin accumulation in the mesangium. Thickening and fragmentation of the basement membrane are observed, resulting from both chronic hyperglycemia and cytokine-induced endothelial activation. Immunohistochemically, overexpression of ICAM-1, vWF, and VEGF is detected, indicating endothelial dysfunction and attempts at compensatory neoangiogenesis. In the tubulointerstitial regions, dense lympho-macrophage infiltrates are observed, consisting of CD3+ T-lymphocytes, CD68+ macrophages, and plasma cells, occasionally with microfoci of necrosis. The epithelium of the proximal tubules frequently exhibits dystrophic and necrotic changes: cytoplasmic vacuolization, nuclear pyknosis, loss of the brush border, and mitochondrial destruction, indicating ischemic-toxic injury. In some cases, the presence of SARS-CoV-2 antigens in podocytes and proximal tubular cells is immunohistochemically confirmed, demonstrating direct viral invasion of renal tissue. Electron microscopy reveals virus-like particles in endothelial cells and podocytes, as well as alterations of the glomerular filtration barrier – fusion of podocyte foot processes, rupture of the basement membrane, and reduction of fenestrations.

In patients with diabetic nephropathy, additional features include nodular glomerulosclerosis (Kimmelstiel-Wilson type), hyalinosis of afferent arterioles, mesangial cell hyperplasia, and glycoprotein deposits in vascular walls, which exacerbate the course of COVID-19 through progressive impairment of microcirculation. Such patients have an especially high risk of developing acute tubular necrosis in the setting of hypoxia, hypovolemia, or cytokine-mediated endotheliitis. Immunohistochemical studies demonstrate activation of pro-inflammatory and fibrogenic pathways: increased expression of TGF-β, IL-6, TNF-α, and Caspase-3,

indicating apoptosis of tubular cells and initiation of fibrosis. At the same time, reduced expression of E-cadherin is detected, serving as a morphological marker of epithelial-mesenchymal transition – a key process in the development of tubulointerstitial fibrosis.

In the terminal stages of CKD or diabetic kidney disease in COVID-19, total glomerulosclerosis, foci of tubular atrophy, interstitial fibrosis, reduction of the vascular bed, and depletion of nephrons are observed, morphologically confirming the progression of nephrosclerosis. These changes are accompanied by accumulation of lipid droplets in podocytes, degeneration of vascular smooth muscle cells, and endothelial destruction, indicating a metabolic-hypoxic type of multiorgan injury.

Thus, pathomorphological examination of COVID-19-induced lesions is of exceptional importance in the context of polymorbidity, in which the interaction between viral infection, systemic inflammation, and chronic somatic diseases forms a complex pathogenetic continuum. Morphological analysis of organs, primarily the lungs, heart, liver, kidneys, and vascular system, allows identification of specific virus-induced alterations, assessment of parenchymal damage, and determination of mechanisms of mutual aggravation in comorbid conditions. It is morphological studies that provide objective confirmation of the relationship between systemic inflammation and multiorgan injury, enabling differentiation between direct viral cytopathic effects and secondary injuries caused by decompensation of metabolic processes or drug toxicity. Their results have not only scientific but also clinical-prognostic value, as they allow evaluation of the irreversibility of morphological changes, prediction of multiorgan failure, and determination of optimal therapeutic strategies—from anti-inflammatory and anticoagulant to organ-protective therapy. Pathomorphological examination in COVID-19 patients with polymorbid pathology is a key instrument for comprehensive understanding of the disease pathogenesis, integrating fundamental and clinical medicine. Its relevance is determined by its capacity not only to elucidate mechanisms of injury, but also to provide a morphological foundation for a personalized approach to managing patients with severe comorbid conditions, aimed at preventing complications and reducing mortality.

CHAPTER 2
MATERIALS AND METHODS OF THE RESEARCH

2.1. Clinical characteristics of the examined patients

The study of the frequency, structure, and probable genesis of anemic syndrome (AS) in patients with coronavirus disease, as well as the features of the clinical course of COVID-19 infection in the presence of concomitant anemia of varying severity, is based on a retrospective analysis of 870 medical records of patients who underwent inpatient treatment for verified coronavirus disease (COVID-19) in the therapeutic departments of the Regional Municipal Non-Profit Enterprise "Chernivtsi Regional Hospital for War Veterans" during 2020-2021.

All cases of COVID-19 were confirmed using polymerase chain reaction (PCR), in accordance with the protocols approved by the Ministry of Health of Ukraine and the recommendations of the World Health Organization.

In 2022, the World Health Organization updated the criteria for the classification of COVID-19 cases, defining three main categories: suspected, probable, and confirmed cases. These classifications are applied for epidemiological surveillance purposes and are not intended to serve as the basis for clinical decision-making regarding treatment.

1. Suspected case

Individuals are classified as suspected cases if they meet at least one of the following criteria:

1.1. Clinical or epidemiological criteria:

Acute onset of fever and cough

or

Acute onset of at least three of the following symptoms: fever, cough, general weakness, headache, myalgia, sore throat, rhinorrhea, dyspnea, nausea/anorexia/diarrhea

or

Presence of an epidemiological link: contact with a probable or confirmed case, or association with a COVID-19 cluster

1.2. Patients with severe acute respiratory infection:

Fever ≥38 °C and cough for ≤10 days requiring hospitalization

2. Probable case

Probable cases include:

Individuals who simultaneously exhibit clinical symptoms of COVID-19 and have had contact with a probable or confirmed case, or are epidemiologically linked to a COVID-19 cluster

Death of an adult from an unspecified cause with preceding respiratory failure and an epidemiological link to a COVID-19 case

3. Confirmed case

A case is considered confirmed if at least one of the following criteria is met:

A positive result of NAAT (e.g., PCR test) detecting SARS-CoV-2 RNA, regardless of symptoms or exposure history

A positive result of an antigen rapid diagnostic test (Ag-RDT) in a patient meeting relevant clinical or epidemiological criteria

Verification of the COVID-19 diagnosis for inclusion of patients in the study was carried out in accordance with the criteria of the World Health Organization outlined in "Public Health Surveillance for COVID-19 - Case Definitions (2022.1)", as well as Order №762 of the Ministry of Health of Ukraine dated April 2, 2020, "On the Approval of the Protocol 'Provision of Medical Care for the Treatment of Coronavirus Disease (COVID-19)'." A case was considered confirmed if the individual met one of the following diagnostic criteria:

- a positive test result for SARS-CoV-2 nucleic acid detection, including PCR (NAAT), regardless of the presence of clinical symptoms or epidemiological linkage;
- the presence of clinical symptoms of COVID-19 (fever, cough, weakness, headache, myalgia, sore throat, dyspnea, gastrointestinal symptoms) combined with a positive result of a WHO-approved SARS-CoV-2 antigen rapid diagnostic test (Ag-RDT), intended for professional or self-testing use;
- in selected cases – confirmation of COVID-19 based on a combination of clinical criteria and epidemiological linkage (contact with a confirmed case or association with a cluster) together with a positive Ag-RDT result.

Patients who met only the criteria for a suspected or probable case without laboratory confirmation (via NAAT or Ag-RDT) were not included in the primary study cohort. For all included patients, the diagnosis of COVID-19 was laboratory-verified, ensuring the homogeneity of the study sample in accordance with WHO epidemiological standards.

To ensure the homogeneity of the study sample and to minimize the influence of comorbid conditions that could independently affect erythropoiesis or iron metabolism, patients who met at least one of the following criteria were excluded from the analysis:

- history of oncohematological pathology, including multiple myeloma, lymphoproliferative disorders, acute or chronic leukemias, myelodysplastic syndrome, or aplastic anemia;
- chronic kidney disease (CKD) stages IV-V, including patients undergoing maintenance hemodialysis or those with erythropoietin-dependent anemia of nephrogenic origin;
- active or recently completed chemotherapy or radiotherapy (within ≤3 months), which could affect bone marrow hematopoiesis;
- history of massive bleeding or acute blood loss, which could result in post-hemorrhagic anemia independent of the infectious process; laboratory-confirmed vitamin B12 or folate deficiency requiring specific treatment
- chronic autoimmune hemolytic anemia or thalassemias, which have a genetically determined course and are unrelated to COVID-19

Anemia was defined as a hemoglobin level <130 g/L in men and <120 g/L in women. The mean age of patients in the analyzed medical records was 51.5±3.24 years (range: 42-68 years). The gender distribution consisted of 540 (62.07%) men and 330 (37.93%) women.

The study of gender and age characteristics of morbidity and clinical course of viral community-acquired pneumonia associated with SARS-CoV-2 infection (CAP-S) through comparison with community-acquired viral-bacterial pneumonias (CAP-VB) of other etiologies among residents of the Chernivtsi region was based on a retrospective analysis of 200 inpatient medical records of patients with moderate community-acquired pneumonia who were treated in the infectious diseases and pulmonology departments of the Regional Municipal Non-Profit Enterprise "Chernivtsi Regional Clinical Hospital" during 2020-2022.

Depending on the etiological factor, the patients were divided into two groups:

- group 1 – 100 medical records of patients with CAP-S
- group 2 – 100 medical records of patients with community-acquired pneumonia of other viral-bacterial etiologies (influenza, parainfluenza, RSV with bacterial coinfections)

All patients had moderate-severity pneumonia, corresponding to the third group, established based on a range of classical subjective and objective clinical symptoms and findings from chest radiography or chest CT (interstitial and infiltrative changes of segmental, polysegmental, or partial confluent type).

The age of patients with community-acquired pneumonia ranged from 35 to 73 years (mean age 54.2±5.6 years). In Group 1, 38.0% were men and 62.0% were women. In Group 2, 47.0% were men and 53.0% were women. The duration of illness was at least 7 days from the onset of COVID-19 symptoms.

Diagnosis and treatment of community-acquired pneumonia were carried out in accordance with the recommendations of the Evidence-Based Adapted Clinical Guideline "Community-Acquired Pneumonia in Adults: Etiology, Pathogenesis, Classification, Diagnosis, Antimicrobial Therapy, and Prevention" (2019).

Inclusion criteria for the study: hospitalized patients of infectious diseases and pulmonology departments; age 18–90 years; diagnosis of community-acquired pneumonia of SARS-CoV-2 or viral-bacterial etiology of moderate severity; signed informed consent form.

Exclusion criteria: diagnosis of community-acquired pneumonia of SARS-CoV-2 or viral-bacterial etiology of severe severity; mental illness; pregnancy; lactation.

Table 2.1.1 presents the distribution of community-acquired pneumonia cases by age and sex. According to the obtained data, both CAP-S and CAP-VB occurred predominantly in women (62.0% and 53.0%, respectively), whereas men were more frequently affected by CAP-VB (47.0% vs. 38.0%).

Table 2.1.1

Distribution of the examined patients with community-acquired pneumonia by gender and age

Research groups	CAP-S, n=100		CAP-VB, n=100	
	n	%	n	%
Males	38	38,0	47	47,0
Females	62	62,0	53	53,0
Age <50	27	27,0	41	41,0
Age 51-75	51	51,0	35	35,0
Age >75	22	22,0	24	24,0

According to the age distribution, individuals aged 51 to 75 years were more frequently affected by CAP-S (51.0%), whereas younger individuals were more commonly affected by CAP-VB (41.0%).

Patients with severe community-acquired pneumonia and pregnant women were not included in the study.

The characteristics of the main complaints and findings from the physical examination are given in Table 2.1.2.

Table 2.1.2

Frequency of complaints among the examined patients with community-acquired pneumonia

Clinical manifestations	CAP-S, %	CAP-VB, %
Pain in chest	84,0	42,0
Cough	92,0	83,0
Sputum production	87,0	81,0
Dyspnea	81,0	46,0
Fever	98,0	57,0
Headache	59,0	27,0
Loss of consciousness	28	3
Anosmia	62,0	11,0
Fatigue	98,0	27,0
Myalgia	74,0	15,0
Thore throat	26,0	1,0
Nausea, vomiting	59,0	27,0
Diarrhea	43,0	5,0

The distribution of patients with community-acquired pneumonia according to the degree of lung involvement is presented in Table 2.1.3.

Table 2.1.3

Frequency of unilateral and bilateral pneumonia, and reactive pleuritis among the examined patients with community-acquired pneumonia

Clinical manifestations	CAP-S, %	CAP-VB, %	OR
Unilateral	31,0	69,0	0,44* CI [0,27-0,75]
Bilateral	66,0	34,0	1,94* CI [1,18-3,19]
Pleurisy	57,0	9,0	6,33* CI [2,98-13,48]

2.2. Research methods

From the selected inpatient and outpatient medical records, data from patient interviews, physical examination findings, and results of general clinical, biochemical, and instrumental investigations were extracted. Complaints, medical history, and lifestyle characteristics, including the nature of physical activity with consideration of occupation and engagement in sports, were analyzed.

The scope of laboratory investigations included: complete blood count and urinalysis, rapid plasma regain (RPR) test, blood glucose levels, coprological examination, biochemical blood analysis (proteinogram, coagulation profile, lipid spectrum, serum amylase activity, ionogram, blood urea, creatinine, uric acid levels, biochemical markers of hepatic and renal function, and markers of inflammatory activity such as C-reactive protein), all performed using standardized methods approved by the Ministry of Health of Ukraine.

A comprehensive clinical blood test was performed using a hematology analyzer, with calculation of the following parameters: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and hematocrit (HCT).

Diagnosis of SARS-CoV-2 infection was carried out by detecting viral ribonucleic acid using a molecular diagnostic test system intended for qualitative identification of RNA specific to the 2019 nCoV coronavirus. Target genes N, E, and RdRP were detected in clinical specimens (nasopharyngeal and oropharyngeal swabs) obtained from the patient. Detection was performed using real-time reverse transcription polymerase chain reaction (RT-PCR), with subsequent amplicon identification via fluorescent labeling, in the diagnostic laboratories DILA, Esculab, Synevo, and in the Virology Laboratory of the Regional Sanitary and Epidemiological Station (Chernivtsi).

Sputum culture for microbiota and antibiotic susceptibility testing was performed by collecting sputum after deep expectoration, initially before the administration of antibacterial agents, and subsequently two more times. After identification of the etiological agent (in a concentration exceeding 10^6 CFU/mL), its antibiotic susceptibility was determined. The microorganisms isolated from sputum by culture included: Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Streptococcus spp., coagulase-negative staphylococci, Enterobacteriaceae,

Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis, Candida spp., Corynebacterium spp., Neisseria spp., Aspergillus, and Candida.

Among instrumental diagnostic methods, patients underwent chest X-ray or chest computed tomography, ECG, abdominal ultrasonography (liver, spleen, gallbladder, pancreas), ECG, pulse oximetry, and computer spirometry.

Pulmonary function parameters were assessed using a computerized spirometer "BTL-08 SpiroPro" (United Kingdom). Pulmonary function testing was performed in the morning or after a 30-minute rest prior to examination. Data were evaluated considering atmospheric pressure, relative humidity, and ambient temperature. Each patient performed three attempts, of which the highest values were recorded. The following parameters characterizing lung ventilation capacity and bronchial patency were measured: VC – vital capacity; FEV_1 - forced expiratory volume in one second, FVC – forced vital capacity, FEV_1/FVC ratio.

To assess liver function, the following biochemical tests were performed: total bilirubin, concentrations of conjugated and unconjugated bilirubin, thymol turbidity test, proteinogram, coagulation profile, blood lipid spectrum, and the activity of the following enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), as well as blood urea and creatinine levels. These parameters were determined using standardized methods approved by the Ministry of Health of Ukraine.

The severity of community-acquired pneumonia was assessed using the **CRB-65 score**.

The CRB-65 scale evaluates four parameters – consciousness impairment, respiratory rate, systolic and diastolic blood pressure, and patient age.

Symptoms and signs (1 point for each of the following):

confusion (C – Confusion)

respiratory rate ≥ 30/min (R – Respiratory rate)

systolic BP < 90 mmHg or diastolic BP ≤ 60 mmHg (B – Blood pressure)

age > 65 years (65)

Interpretation:

0 points – mild course (mortality 1.2%)

1-2 points – moderate course (mortality 8.15%)

3-4 points – severe course (mortality 31.0%)

All examined patients had pneumonia of moderate severity.

Statistical analysis of the obtained results was performed in accordance with the study design and the types of numerical data collected. Normality of distribution was assessed using the Lilliefors and Shapiro-Wilk tests, as well as by direct visual inspection of distribution histograms. Discrete variables were presented as absolute and relative frequencies (percentage of observations relative to the total number of patients). For comparison of normally distributed data, parametric tests were applied, including Student's t-test and Fisher's F-test. In cases of non-normal distribution, the median test and the Mann-Whitney U test were used; for multiple comparisons of dependent groups, the Wilcoxon T-test was applied.

For comparison of categorical variables, the odds ratio (OR) and relative risk (RR) were calculated with a 95% confidence interval (CI). Odds ratios were considered statistically significant at $p<0.05$. Calculations were performed using the licensed software Past3. Statistical and graphical analyses were conducted using Statistica for Windows v.10.0 (StatSoft Inc., USA) and Microsoft Excel 2016 (Microsoft, USA).

The research adhered to internationally and nationally accepted ethical and regulatory guidelines, including:

- the main standards of Good Clinical Practice (GCP, 1996)
- the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997)
- the Declaration of Helsinki of the World Medical Association on ethical principles for medical research involving human subjects (1964-2004)
- the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences (CIOMS)
- orders of the Ministry of Health of Ukraine №281 (01.11.2000), №66 (13.02.2006), and №142 (22.03.2007).

CHAPTER 3
EPIDEMIOLOGICAL AND CLINICAL PATTERNS AND MORPHOLOGICAL CORRELATES OF MORTALITY FROM COVID-19 IN THE CHERNIVTSI REGION (2020-2022)

The analysis of mortality from complications associated with COVID-19 among the population of the Chernivtsi region and the city of Chernivtsi is based on a retrospective study of archival materials from the Department of Forensic Medical Examination of Corpses of the State Institution "Chernivtsi Regional Bureau of Forensic Medical Examination" for the period from 2020 to 2022. The aim of the study was to identify demographic patterns, clinicopathological characteristics, and leading causes of death among individuals who died as a result of COVID-19 complications, followed by an assessment of the impact of comorbid conditions on fatal outcomes.

The study was conducted in accordance with the principles of forensic medical analysis using a comprehensive approach that integrated clinical, laboratory, epidemiological, and morphological data. A total of 152 fatal cases registered during the specified period were included. For each case, a systematic evaluation of the following parameters was performed:

- demographic characteristics (age, gender, place of residence);
- clinical data (medical history, presence of chronic diseases, duration of hospitalization);
- pathological and morphological findings obtained during autopsy;
- results of PCR testing for SARS-CoV-2 to confirm the viral etiology of the disease.

Additionally, hospitalization conditions, the time from symptom onset to death, and the coexistence of infectious lesions with concomitant somatic pathology were analyzed. The collected data were summarized using analytical and comparative statistical methods.

The analysis demonstrated a gender-related heterogeneity among individuals who died from COVID-19 complications. Among the 152 cases examined, men predominated – 90 individuals (59%), whereas women accounted for 62 cases (41%) (Fig. 3.1). This distribution is consistent with global epidemiological trends indicating that mortality and disease severity in COVID-19 are higher among men. Scientific studies suggest that this difference may be explained by a combination of biological, immunological, and behavioral factors.

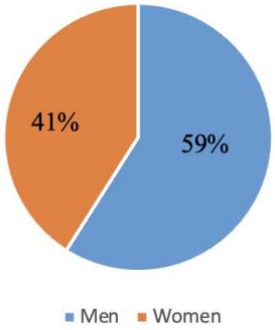


Fig. 3.1. Gender distribution among deceased individuals with COVID-19

Such an uneven sex distribution can likely be explained by the fact that men naturally have lower levels of estrogens, which possess immunomodulatory and anti-inflammatory properties, as well as reduced activity of the TLR7-dependent signaling pathway responsible for recognizing single-stranded viral RNA, including SARS-CoV-2. In addition, males more frequently suffer from concomitant cardiometabolic disorders (arterial hypertension, ischemic heart disease, obesity, and type 2 diabetes mellitus) which increase the risk of fatal outcomes. Behavioral and social factors also play an important role, particularly the higher prevalence of smoking, alcohol misuse, delayed medical consultation, and poorer adherence to treatment regimens.

The mean age of the deceased was 63.4 years, and the median age was 68.5 years, reflecting the typical profile of patients prone to severe COVID-19. The age range was extremely broad; however, most fatal cases occurred in the 61-75-year age group (46 individuals, 30.3%) and the 76-90-year age group (47 individuals, 30.9%), together accounting for 61% of the total sample. This distribution is consistent with the pathophysiological features of aging, which include reduced reserve capacity of the immune and respiratory systems, endothelial dysfunction, and increased susceptibility to hypercoagulation.

At the same time, the proportion of working-age individuals among the deceased was also considerable: 14 cases (9.2%) in the 31-45-year age group and 34 cases (22.4%) among individuals aged 46-60 years, indicating substantial involvement of the active population in the risk group. This highlights that COVID-19 is not confined exclusively to elderly patients, and its complications may be fatal even for middle-aged individuals, particularly in the presence of concomitant metabolic or cardiovascular disorders.

The high median age (68.5 years) underscores the key role of age as one of the strongest predictors of poor prognosis in COVID-19. Older individuals exhibit atrophy of the alveolar epithelium, reduced elasticity of lung tissue, endothelial rigidity, and immunological dysregulation with altered CD4+/CD8+ T-cell ratios, decreased interferon levels, and reduced antibody production. These changes lead to diminished antiviral defense, prolonged viremia, and a tendency toward a hyperinflammatory reaction (“cytokine storm”), which complicates the course of SARS-CoV-2 infection even with timely diagnosis and adequate therapy.

A positive PCR test result for SARS-CoV-2 was registered in the majority of the deceased – 51% of cases – confirming the reliable etiological role of the virus in the development of fatal complications. Meanwhile, in 44 cases (approximately 29%), PCR tests were negative; however, forensic examination revealed typical morphological features of COVID-19-associated pneumonia, including diffuse alveolar damage, hyaline membranes, microthromboses, and proliferation of type II alveolocytes. This suggests that a negative test result does not exclude the presence of current or past COVID-19, particularly in late-stage or post-infectious periods when viral replication is minimal but immune-inflammatory lesions persist.

The likely causes of such discrepancies between clinical-laboratory and morphological findings are multifactorial. First, late testing, performed after the peak of viremia, reduces the likelihood of detecting viral RNA in samples taken from the upper respiratory tract, particularly in patients with a prolonged course of infection. In such cases, the virus may already be eliminated from the mucosal surfaces but persist in the lower respiratory tract or tissues not covered by routine testing. False-negative PCR results may also result from an insufficient amount of viral material, improper sample collection technique, low sensitivity of certain diagnostic kits, or violations of transportation and storage conditions. According to several studies, the sensitivity of PCR for SARS-CoV-2 may range from 63% to 78%, depending on the time elapsed since symptom onset, indicating a potentially high rate of false-negative results in clinical practice.

Additionally, the presence of post-infectious complications such as hypercytokinemia, disseminated intravascular coagulation, or nosocomial bacterial infections may become the direct cause of death after viral elimination. In such cases, the morphological picture retains features of COVID-19-induced injury (particularly the fibrotic-proliferative phase of diffuse alveolar damage), whereas PCR results are already negative. It is important to consider the possibility of a protracted course or persistent inflammatory response following acute infection, in which immunopathological processes rather than active viral replication constitute the primary mechanism of lung parenchymal injury. This aligns with current concepts of post-COVID hyperinflammatory syndrome, which morphologically manifests as macrophage activation, endothelial swelling, fibrosis, and vasculitis even in the absence of detectable viral RNA.

The presence of negative testing results in patients with a typical morphological pattern of COVID-19 underscores the need for a comprehensive diagnostic approach that integrates clinical, laboratory, epidemiological, and pathomorphological data. This is particularly critical in retrospective analyses of fatal cases, in which morphological verification of viral injury remains the “gold standard,” allowing clarification of the true causes of death and correction of statistical reports on actual COVID-19 mortality.

A retrospective analysis of 152 fatal cases of COVID-19 among residents of the city of Chernivtsi and the Chernivtsi region revealed several patterns regarding the structure of comorbid conditions that significantly influenced disease severity, the development of complications, and overall prognosis. The results show that the vast

majority of deceased patients had multiple comorbidities that served as a pathogenetic background, exacerbating the consequences of the viral infection.

Among the examined individuals, cardiovascular pathology was most frequently reported, particularly arterial hypertension identified in 11 cases (7.2%). In many patients, it coexisted with ischemic heart disease, myocardial hypertrophy, and heart failure. The presence of chronic hypertension created preconditions for the development of endothelial dysfunction, microcirculatory disturbances, and a hypercoagulable state, which, in the context of SARS-CoV-2 infection, contributed to the formation of microthrombi in the pulmonary vasculature and to the worsening of tissue hypoxia. Morphologically, these patients often exhibited thickening of arteriolar walls, endothelial swelling, perivascular infiltrates, and fibrinoid necrosis of the vascular wall.

Type 2 diabetes mellitus was identified in 7 individuals (4.6%) and was characterized by typical manifestations of diabetic microangiopathy. Impaired carbohydrate metabolism likely intensified oxidative stress, reduced the effectiveness of the immune response, and increased susceptibility to secondary bacterial infections. Clinically, this manifested as a prolonged course of pneumonia, elevated levels of procalcitonin and C-reactive protein (according to medical records), while morphologically, multiple capillary microthromboses, vascular hyalinosis, and interalveolar septal edema were observed.

Atherosclerosis and obesity, documented in 8 patients (5.3%), represent a metabolically inflammatory comorbidity phenotype characterized by dyslipidemia, endothelial activation, and elevated levels of IL-6 and TNF-α. Excess adipose tissue functions as an active endocrine organ that produces pro-inflammatory cytokines, thereby sustaining chronic systemic inflammation. In such patients, post-mortem examination revealed diffuse interstitial edema, fibrosis, fat embolism, and perivascular macrophage infiltration, indicating the role of obesity as a factor that amplifies inflammatory responses in COVID-19.

Chronic interstitial nephritis was identified in 2 cases (1.3%), accompanied by reduced glomerular filtration and tubular injury. It is well established that pre-existing renal dysfunction markedly reduces the body's adaptive reserves under systemic hypoxia and increases the risk of acute kidney injury during viral infection. Morphologically, this manifested as glomerular capillary endotheliosis, microthrombosis of capillary loops, interstitial infiltrates, and tubular epithelial dystrophy.

It is important to note that even in cases where comorbid conditions were only partially documented (approximately 18% of all autopsies), their impact on the severity of COVID-19 was evident. In most remaining cases (82%), a combination of features of metabolic syndrome, chronic cardiopulmonary, or hepatorenal disorders was identified, although without clear clinical verification. This highlights the need for more systematic collection of medical history data, standardization of comorbidity reporting, and integration of morphological findings into the clinicopathological assessment of fatal cases.

Thus, the obtained results confirm that comorbidity is a key determinant of severe COVID-19. It defines the extent of endothelial dysfunction, inflammatory activation, thrombotic injury, and multiorgan failure, ultimately shaping an unfavorable clinical prognosis. A comprehensive analysis of the comorbid background combined with morphological data is essential for developing stratified preventive and therapeutic strategies in SARS-CoV-2 infections.

CHAPTER 4
CLINICAL FEATURES OF COMMUNITY-ACQUIRED PNEUMONIA ASSOCIATED WITH COVID-19

4.1. Age and gender characteristics of community-acquired pneumonia associated with COVID-19 and community-acquired pneumonia of other viral-bacterial etiology

All cases of community-acquired pneumonia (CAP) of moderate severity were hospitalized upon referral from family physicians due to their classification as Group 3 CAP.

An analysis of CAP incidence showed that women were more frequently hospitalized with CAP associated with SARS-CoV-2 (CAP-COV), accounting for 62.0% of cases versus 38.0% among men ($p<0.05$). At the same time, among patients with viral-bacterial CAP of non-COVID etiology, the female-to-male ratio was 53.0% versus 47.0% ($p>0.05$) (Table 4.1.1).

Table 4.1.1

Incidence of CAP associated with COVID-19 and community-acquired pneumonia of other viral-bacterial origin depending on sex and age (n, %)

Research group	CAP-S, n=100		CAP-VB, n=100		OR, %
	N	%	N	%	
Males	38	38,0	47	47,0	0,81 CI [0,48-1,36]
Females	62	62,0	53	53,0	1,17* CI [0,74-1,85]
Age <50	27	27,0	51	51,0	1,89* CI [1,09-3,25]
Age 51-75	49	49,0	25	25,0	1,96* CI [1,12-3,42]
Age >75	24	24,0	24	24,0	1,0 CI [0,53-1,88]

According to the age distribution, individuals aged 51 to 75 years were more frequently affected by COVID-19-associated CAP (CAP-S), accounting for 49.0% of cases (OR=1.96; CI [1.12-3.42]) ($p<0.05$), whereas younger individuals <50 years were more often affected by viral-bacterial CAP of non-COVID etiology (51.0%) (OR=1.89; CI [1.09-3.25]) ($p<0.05$).

The age category >75 years showed an equal incidence of CAP-S and non-COVID viral-bacterial CAP (OR =1.0; CI [0.53-1.88]) ($p>0.05$).

4.2. Clinical features of community-acquired pneumonia associated with COVID-19 and viral-bacterial community-acquired pneumonia of other etiology

Analysis of the frequency of clinical symptoms of CAP demonstrated a statistically significant difference in the following parameters: intense chest pain during

breathing and coughing was reported 2.0 times more frequently in patients with COVID-19-associated CAP compared with non-COVID viral-bacterial CAP (OR=2.0; CI [1.26-3.18]) ($p<0.05$); fever occurred 1.7 times more often (OR=1.72; CI [1.12-2.63]) ($p<0.05$) (Table 4.2.1). Anosmia was reported 5.6 times more frequently in patients with COVID-19-associated CAP (OR=5.64; CI [2.80-11.33]) ($p<0.05$). The frequency of cough was comparable between the two groups (OR=1.11; CI [0.73-1.66]) ($p>0.05$).

The frequency of dyspnea with progressively increasing intensity was observed 1.7 times more often in patients with CAP-S compared with CAP of other viral-bacterial etiology (OR=1.76, CI [1.12-2.78], $p<0.05$). Myalgias occurred 4.9 times more frequently (OR=4.93, CI [2.65-9.17], $p<0.05$). Marked general weakness followed by prolonged asthenia was recorded 3.6 times more frequently in patients with CAP-S than in those with CAP of mixed viral-bacterial origin (OR=3.63, CI [2.18-6.03], $p<0.05$).

Table 4.2.1.

Frequency of reported complaints in examined patients with community-acquired pneumonia associated with COVID-19 and community-acquired pneumonia of other viral-bacterial etiology (n, %)

Clinical signs	CAP-S, n=100	CAP-VB, n=100	OR
Pain in chest	84	42	2,0* ДІ [1,26-3,18]
Cough	92	83	1,11 ДІ [1,26-3,18]
Sputum discharge	87	81	1,20 ДІ [0,45-1,69]
Dyspnea	81	46	1,76* ДІ [1,12-2,78]
Fever	98	57	1,72* ДІ [1,12-2,63]
Headache	59	27	2,19* ДІ [1,28-3,72]
Loss of consciousness	28	3	9,33* ДІ [2,75-31,69]
Anosmia	62	11	5,64* ДІ [2,80-11,33]
Fatigue	98	27	3,63* ДІ [2,18-6,03]
Myalgia	74	15	4,93* ДІ [1,65-9,17]
Sore throat	26	1	26,0* ДІ [3,46-195,30]
Nausea, vomiting	59	27	2,19* ДІ [1,28-3,72]
Diarrhea	43	5	8,60* ДІ [3,27-22,61]

Intense headache at disease onset was documented 2.2 times more often in CAP-S patients (OR=2.19, CI [1.28-3.72], $p<0.05$). Short episodes of loss of consciousness were observed 9.3 times more frequently in CAP-S (OR=9.33, CI [2.75-31.69], $p<0.05$). Severe sore throat with odynophagia was recorded 26-fold more often in CAP-S (OR=26.0, CI [3.46-195.30], $p<0.05$). Nausea occurred 2.2 times more frequently (OR=2.19, CI [1.28-3.72], $p<0.05$), while diarrhea was noted 8.6 times more often in CAP-S compared with CAP of other viral-bacterial etiology (OR=8.6, CI [3.27-22.61], $p<0.05$) (see Table 4.2.1).

Analysis of objective clinical findings and laboratory parameters revealed statistically significant differences in the following indicators (Table 4.2.2): a larger proportion of patients with CAP-S, compared with CAP of other viral-bacterial origin, had elevated body temperature above 38.5°C (OR=2.38, CI [1.44-3.91], p<0.05); heart rate exceeding 90 beats per minute (OR=2.6, CI [1.57-4.30], p<0.05); and respiratory rate greater than 25 breaths per minute (OR=2.86, CI [1.64-5.01], p<0.05).

Table 4.2.2

Frequency of identified objective clinical symptoms in patients with community-acquired pneumonia associated with COVID-19 and community-acquired pneumonia of other viral-bacterial etiology (n, %)

Clinical signs	CAP-S, n=100	CAP-VB, n=100	OR
Fever above 38°C	76	32	2,38* ДІ [1,44-3,91]
HR >90 bpm	78	30	2,60* ДІ [1,57-4,30]
BR >25 per min	63	22	2,86* ДІ [1,64-5,01]
Sp O_2 90-92%	85	49	1,73* ДІ [1,11-2,71]

Patients with CAP-S demonstrated a 1.7-fold higher frequency of reduced oxygen saturation values within the range of 90–92% compared with those with CAP of other viral-bacterial etiology (OR=1.73, CI [1.11-2.71], p<0.05) (see Table 4.2.2).

Analysis of the frequency of hematological parameters in patients with community-acquired pneumonia associated with COVID-19 and those with community-acquired pneumonia of other viral-bacterial origin indicates a significant damaging effect of SARS-CoV-2 on leukocytes, lymphocytes, and platelets. Thus, leukopenia below 4.0x10^9/L was detected in 65.0% of patients with CAP-S versus 32.0% of those with CAP of mixed viral-bacterial etiology (OR=2.03, CI [1.23-3.37], p<0.05) (Table 4.2.3). Similarly, lymphocytopenia of varying severity was observed in 87.0% of CAP-S patients compared with 27.0% in the CAP-VB group (OR=3.22, CI [1.93-5.38], p<0.05). Thrombocytopenia was also significantly more common in CAP-S, recorded in 69.0% of patients versus 31.0% in the CAP-VB group (OR=2.23, CI [1.34-3.69], p<0.05) (see Table 4.2.3).

Analysis of biochemical markers reflecting the intensity of inflammation (Table 4.2.3) demonstrated a higher frequency of hyperfibrinogenemia (OR=2.66, CI [1.62-4.34], p<0.05) and hyperferritinemia (OR=3.72, CI [2.06-6.71], p<0.05) in patients with CAP-S.

Table 4.2.3

Frequency of identified laboratory and biochemical inflammatory markers in patients with community-acquired pneumonia associated with COVID-19 and community-acquired pneumonia of other viral-bacterial etiology (n, %)

Clinical signs	CAP-S, n=100	CAP-VB, n=100	OR
WBC < 4,0 G/L	65	32	2,03* CI [1,23-3,37]
Lymphocytes < 0,9 G/L	87	27	3,22* CI [1,93-5,38]
Platelets < 1,2 G/L	69	31	2,23* CI [1,34-3,69]
Fibrinogen >5,0 g/L	85	32	2,66* CI [1,62-4,34]
CRP >20,0 mg/L	95	37	2,57* CI [1,60-4,11]
ESR >20 mm/h	54	28	1,93* CI [1,13-3,29]
Ferritin >300,0 mcg/L	67	18	3,72* CI [2,06-6,71]

In patients with COVID-19-associated pneumonia, a higher frequency of elevated C-reactive protein (CRP) levels above 20 mg/L was recorded – 2.6 times higher (OR=2.57, CI [2.76-52.13]) ($p<0.05$), as well as a higher frequency of increased ESR above 15 mm/h – 1.9 times higher (OR=1.93, CI [1.13-3.29]) ($p<0.05$) (see Table 4.2.3). The above findings indicate that COVID-19 triggers a systemic inflammatory response of considerable intensity, significantly exceeding the inflammatory activity observed in viral-bacterial pneumonia.

Analysis of biochemical indicators reflecting the functional status of the liver and kidneys in patients with pneumonia revealed the following changes (Table 4.2.4). Analysis of the figures of pigment metabolism revealed a significant increase in total bilirubin levels in patients of Group 1 – by 1.9 times, and in Group 2 – by 1.2 times ($p<0.05$) compared with the group of practically healthy individuals, which indicates the hepatotropic properties of SARS-CoV-2 and its ability to damage hepatocytes.

Analysis of the distribution of total bilirubin fractions demonstrates an increase in the conjugated fraction in Group 1 patients by 1.7 times ($p<0.05$) and of the unconjugated fraction by 2.0 times ($p<0.05$) (see Table 4.2.4). Thus, disturbances of bilirubin metabolism in patients with COVID-19-associated pneumonia reflect the pathogenetic hepatotropic impact of the virus, which contributes to the severity of the patient's condition.

ALT activity in Group 1 patients exceeded the values in practically healthy individuals by 3.5 times ($p<0.05$), and AST activity by 2.9 times ($p<0.05$), indicating the presence of a hepatocellular cytolysis syndrome in the CAP-S group and suggesting reactive hepatitis of moderate activity. In Group 1 patients, a reduction in the De Ritis ratio (AST/ALT) by 1.2 times ($p<0.05$) was identified, which points to the presence of hepatitis of viral origin.

In patients of Group 2, the activity of the cytolytic syndrome was significantly lower compared with patients of Group 1. Specifically, ALT activity in Group 2 exceeded the value in practically healthy individuals by 1.8 times ($p<0.05$), while AST

activity exceeded it by 1.4 times ($p<0.05$), and both indicators differed significantly from those in Group 1 ($p<0.05$). Under these conditions, the De Ritis ratio (AST/ALT) was 1.3 times lower than in practically healthy individuals ($p<0.05$), indicating the development of an inflammatory liver disease likely of viral origin.

Table 4.2.4

Indicators of liver and kidney functional status in patients with community-acquired pneumonia associated with COVID-19 and community-acquired pneumonia of other viral–bacterial etiology (n, %)

Figures	Healthy individuals, n=20	Groups of patients		
		CAP-S, n=100	CAP-VB, n=100	P
Total bilirubin, mcmol/L	18,15±1,25	35,27±1,14	22,51±1,33	P1<0,05 P3<0,05
Direct bilirubin, mcmol/L	4,41±0,18	7,31±0,21	4,78±0,35	P1<0,05 P3<0,05
Indirect bilirubin, mcmol/L	13,86±0,47	27,96±1,09	17,73±1,12	P1<0,05 P3<0,05
AST, mcmol/h×L	0,38±0,01	1,12±0,01	0,52±0,02	P1,2<0,05 P3<0,05
ALT mcmol/h×L	0,37±0,01	1,29±0,02	0,65±0,03	P1,2<0,05 P3<0,05
De Ritis ratio	1,03±0,01	0,87±0,01	0,80±0,01	P1,2<0,05 P3<0,05
GGT, mmol/h×L	5,18±0,12	6,54±0,12	5,46±0,15	P1<0,05 P3<0,05
ALP, mmol/h×L	1,21±0,01	1,63±0,01	1,33±0,01	P1<0,05 P3<0,05
Thymol test, IU	2,55±0,17	4,72±0,13	3,25±0,15	P1,2<0,05 P3<0,05
Fibrinogen, g/L	3,23± 0,11	7,37±0,15	3,45±0,16	P1<0,05 P3<0,05
Ferritin, mcg/L	53,41±4,15	470,23±6,29	217,36±5,34	P1,2<0,05 P3<0,05
CRP, mg/L	3,02± 0,31	65,28± 4,33	17,31± 1,25	P1,2<0,05 P3<0,05
Creatinine, mcmol/L	68,14± 3,22	137,53± 2,57	84,25± 2,29	P1,2<0,05 P3<0,05
Urea, mmol/L	4,15± 0,35	9,81± 0,54	6,42± 0,31	P1,2<0,05 P3<0,05

Notes:
P1 – the difference is significant for Group 1 compared with healthy individuals;
P2 – the difference is significant for Group 2 compared with healthy individuals;
P3 – the difference is significant compared with patients with COVID-19-associated community-acquired pneumonia (CAP-S).

The presence of a mesenchymal-inflammatory syndrome was indicated by an increase in the thymol test in both comparison groups. In Group 1 patients, it exceeded the level in healthy individuals by 1.9 times, and in Group 2 by 1.3 times ($p<0.05$) (Table 4.2.4). Plasma fibrinogen levels in Group 1 were significantly higher than in healthy individuals by 2.3 times ($p<0.05$), and ferritin levels by 8.9 times compared with a 4.1-fold increase in Group 2 patients. CRP levels exceeded those in healthy individuals by 24.9 times in Group 1 vs. 5.7 times in Group 2. A cholestatic syndrome was identified in patients with CAP-S. An increase in alkaline phosphatase (ALP) activity by 1.3 times ($p<0,05$) compared with healthy individuals, along with a parallel increase in GGT activity also by 1.3 times ($p<0.05$) indicates the presence of cholestasis.

Thus, COVID-19 complicated by community-acquired pneumonia was accompanied by significant liver parenchymal injury with the development of cytolytic, cholestatic, and mesenchymal-inflammatory syndromes of moderate activity.

At the same time, an increase in blood creatinine levels was found in Group 1 by 2.0-fold ($p<0.05$) compared with a 1.2-fold increase in Group 2 ($p<0.05$), indicating the nephrotropic activity of SARS-CoV-2. An increase in blood urea levels was also observed in both groups: in Group 1 by 2.4-fold ($p<0.05$) versus a 1.5-fold increase in Group 2 ($p<0.05$) (see Table 4.2.4). Thus, COVID-19 complicated by CAP was accompanied by significant renal parenchymal injury, with the development of acute kidney injury in some cases and progression of pre-existing CKD in others.

Analysis of chest radiological studies in patients with CAP-S demonstrated that bilateral pneumonia was more frequently observed – 66.0% compared to 34.5% in CAP-VB, which was 1.9 times more common in CAP-S (OR=1.94; CI [1.18-3.19]) ($p<0.05$). Inflammatory pleural reactions were also observed 6.3 times more frequently in CAP-S – 57.0% versus 9.0% in CAP-VB (OR=6.33; CI [2.98-13.48]) ($p<0.05$) (Table 4.2.5).

Table 4.2.5

Frequency of unilateral and bilateral pneumonia, and reactive pleuritis among the examined patients with community-acquired pneumonia

Clinical manifestations	CAP-S, %	CAP-VB, %	OR
Unilateral	31,0	69,0	0,44* CI [0,27-0,75]
Bilateral	66,0	34,0	1,94* CI [1,18-3,19]
Pleurisy	57,0	9,0	6,33* CI [2,98-13,48]

Typical CT features of CAP associated with COVID-19 included multiple lobular opacities of the “ground-glass opacity” type and subsegmental consolidation zones, reflecting homogeneous increases in lung parenchymal density with obscuration of underlying vessels: ground-glass opacity – an area of increased attenuation without vessel obscuration – indicated interlobular septal edema and thickening; ground-glass opacity with a reticular pattern (a reticular shadow overlying ground-glass opacity with thickened lung structures) suggested interlobular septal thickening, forming a subpleural line over time; a sign of microvascular dilation (enlarged small vessels within lesions) indicated increased perfusion of inflamed segments; fibrotic streaks (irregular linear opacities) reflected local inflammatory resorption and residual fibrosis;

subpleural line (an arcuate 2-5 cm linear opacity running parallel to the chest wall) or a subpleural transparent line (a thin lucent line between lesions and the visceral pleura) was also noted.

Lung involvement was classified as predominantly peripheral (one-third of the lung), central (two-thirds), or mixed (peripheral and central).

Bronchial changes were of two types: air bronchogram (air-filled bronchus visible within consolidated lung) and bronchial deformation, suggesting local inflammation and tractional bronchial displacement. Pleural changes were categorized as: pleural retraction signs (lesions adjacent to visceral pleura causing its inward pulling) or pleural effusion. Pleural changes were more frequent in Group 1, whereas bronchial alterations were more typical in Group 2.

Thus, in CAP-S, bilateral multisegmental lung lesions occurred more frequently than unilateral ones and were accompanied by reactive pleural inflammation. In most patients of Group 1, involvement of the lower and middle lung segments was identified. The most common pulmonary changes included fibrotic alterations, "ground-glass opacities" with a reticular pattern, and consolidation. Among bronchial changes, air bronchograms were prevalent, whereas bronchial deformation was less common. Pleural changes most frequently included signs of pleural retraction and pleural thickening.

Table 4.2.6

Changes in pulmonary function parameters in patients with community-acquired pneumonia associated with COVID-19 and community-acquired pneumonia of other viral-bacterial etiology

Figure, %	Research groups			
	Healthy individuals, n=20	CAP-S, n=100	CAP-VB, n=100	P
VC, %	90,23±1,25	75,35±1,32	87,87±1,27	P1<0,05 P3<0,05
FEV_1	91,75±1,93	86,28±1,21	75,12±1,44	P2<0,05 P3<0,05
FEV_1 after salbutamol inhalation, %	98,23±1,54	90,45±1,23	79,30±1,36	P1,2<0,05 P3<0,05
FVC, %	83,31±2,56	85,75±2,15	73,28±2,47	P2<0,05 P3<0,05
FEV_1/FVC, %	110,13±2,42	100,62±2,48	102,51±2,55	P1,2,3>0,05

Notes:
P1 – the difference is significant for Group 1 compared with healthy individuals;
P2 – the difference is significant for Group 2 compared with healthy individuals;
P3 – the difference is significant compared with patients with COVID-19-associated community-acquired pneumonia (CAP-S).

Analysis of pulmonary function test (PFT) results in patients with moderately severe CAP-VB compared with patients with CAP-S demonstrated more pronounced and statistically significant reductions in PFT flow parameters (Table 4.2.6).

In patients of Group 2 the FEV_1 before salbutamol inhalation was significantly lower by 18.1% compared with the value in the healthy individuals ($p<0.05$) (Table 4.2.6). However, the mean FEV_1 values after β-adrenergic agonist inhalation were 19.3% lower than the healthy individuals value ($p<0.05$). The increase in FEV_1 after salbutamol inhalation in patients of Group 2 was 5.6%, indicating an irreversible bronchial obstructive syndrome. In patients of Group 1, flow parameters differed significantly from the healthy individuals only after salbutamol inhalation: FEV_1 was 7.9% lower ($p<0.05$). The FVC changed significantly only in Group 2 being 12.0% below the healthy individuals value ($p<0.05$). Changes observed in Group 1 were not statistically significant. At the same time, in patients of Group 1, a significant decrease in VC by 1.2 times ($p<0.05$) was found, indicating restrictive changes in the lungs due to pneumonia (see Table 4.2.6).

Thus, we concluded that the course of CAP-VB is accompanied by bronchoobstructive syndrome, which is caused by the effect of viral-bacterial infection on the bronchoalveolar system and by sensitization of the organism to pathogens and their metabolic products. A reduced degree of bronchoobstructive syndrome reversibility may also be influenced by comorbid COPD in this patient group ($p<0.05$). Meanwhile, in patients with CAP-S, significant restrictive changes were established, associated with the predominance of bilateral infiltrative lung involvement resulting from the inflammatory process.

Analysis of sputum culture results in patients with viral-bacterial CAP that developed against the background of influenza, parainfluenza, and RSV during the 2023-2024 epidemic season indicates a limited diversity of bacterial pathogens isolated as coinfections or superinfections accompanying the viral pneumonia. Thus, the list of pathogens most frequently cultured from sputum in patients of Group 2 in diagnostically significant titers and having etiological significance in influenza-associated bacterial pneumonia is presented in Table 4.2.7.

The most common pathogens involved in this pneumonia were K. pneumoniae, S. pneumoniae (37.0%), S. pyogenes (22.0%), S. aureus (21.0%), H. influenzae (35.0%), and M. catarrhalis (17.0%), all of which were detected significantly more often compared with CAP-S ($p<0.05$). Thus, CAP occurring on the background of influenza, parainfluenza, or RSV is characterized by substantial coinfection and superinfection, has a mixed viral-bacterial nature, and differs in its clinical course from CAP developing during SARS-CoV-2 infection.

At the same time, the rate of bacterial and fungal co- and superinfections in moderate COVID-19-associated CAP was relatively low, within 17.0% only, whereas in CAP-VB the co- and superinfection index reached 52.0%.

Table 4.2.7

Frequency of detected bacterial and fungal coinfections and superinfections in patients with CAP-S and CAP-VB (n, %)

Infectious agent	CAP-S, n=100	CAP-VB, n=100	OR
K. pneumoniae	10	31	3,10* CI [1,44-6,66]
Streptococcus pneumoniae	11	37	3,36* CI [1,62-6,96]
S. aureus	8	21	2,63* CI [1,11-6,21]
H. influenzae	7	35	5,0* CI [2,12-11,79]
Mycoplasma pneumonia	9	1	9,0* CI [1,12-72,37]
Acinetobacter spp.	4	1	4,0 CI [0,43-36,242]
Escherichia coli	4	13	3,25* CI [1,03-10,31]
Pseudomonas aeruginosa	3	1	3,0 CI [0,31-29,33]
Chlamydia pneumonia	2	8	4,0 CI [0,83-19,31]
M. catarrhalis	2	17	8,5* CI [1,91-37,76]
Bordetella	1	1	1,0 CI [0,06-16,21]
S. pyogenes	1	22	22,0* CI [2,91-166,4]
Aspergillus	8	1	8,0 CI [0,98-65,15]
Candida	2	4	2,0 CI [0,36-11,17]

The specific microorganisms most frequently associated with COVID-19 (see Table 4.2.7) were: Streptococcus pneumoniae (11.0%), K. pneumoniae (10.0%), S. aureus (8.0%), Mycoplasma pneumoniae (9.0%), H. influenzae (7.0%); other bacteria were isolated in the range of 1.0%-4.0%. The most frequent fungi causing coinfections in CAP-S were: Aspergillus spp. (8.0%), Candida spp. (2.0%).

4.3 Structure of comorbid conditions in patients with community-acquired pneumonia associated with COVID-19 and community-acquired pneumonia of other etiology

Analysis of comorbid conditions showed that patients with CAP had a number of modifying factors and risk factors for severe disease progression due to existing comorbid pathology. Thus, patients in Group 1 were twice as likely (42.0%) to have

excess body weight compared with 21.0% in Group 2 (OR=2.0, CI [1.11-3.62]) ($p<0.05$) (Table 4.3.1). At the same time, 13.0% of patients in Group 1 had obesity, which was 4.3 times more frequent than in Group 2 (3.0%) (OR=4.33, CI [1.19-15.67]) ($p<0.05$). Individuals with overweight and obesity have reduced anti-infective immunity; therefore, these comorbidities represent important risk factors for severe CAP.

There was also a higher frequency of type 2 diabetes mellitus in Group 1 compared with Group 2 – 2.7 times higher (OR=2.71, CI [1.09-6.74]) ($p<0.05$). A considerable number of Group 1 patients (49.0%) had hyperlipidemia and dyslipidemia, which are modifiable risk factors for atherosclerosis. In Group 2, these conditions were observed with 2.9 times lower frequency (12.0%) (OR=2.88, CI [1.56-5.34]) ($p<0.05$) (see Table 4.2.1).

Table 4.2.1

Frequency of detected risk factors for severe CAP and comorbid conditions in patients with CAP associated with COVID-19 and community-acquired pneumonia of other etiology (n, %)

Comorbid condition	CAP-S, n=100	CAP-VB, n=100	OR
Smoking	13	31	2,38* CI [1,18-4,82]
BMI 25-29,9 kg/m^2	42	21	2,0* CI [1,11-3,62]
BMI >30 kg/m^2	13	3	4,33* CI I [1,19-15,67]
Arterial hypertension	49	12	4,08* CI [2,05-8,14]
Diabetes mellitus type 2	19	7	2,71* CI [1,09-6,74]
Hyper-, dyslipidemia	49	17	2,88* CI [1,56-5,34]
Bronchial asthma	9	18	2,0 CI [0,86-4,66]
COPD	8	24	3,0* CI [1,29-6,99]
CAD	31	8	3,88* CI [1,69-8,84]
Myocarditis	34	5	6,80* CI [2,55-18,10]
Arrythmia	7	5	1,4 CI [0,43-4,56]
Heart failure	24	9	2,67* CI [1,18-6,02]
Chronic kidney disease	28	6	4,67* CI [1,85-11,76]
Rheumatic diseases	12	7	1,71 CI [0,65-4,53]
Oncological diseases	5	7	1,4 CI [0,43-4,56]
Hepatitis	41	6	6,80* CI [2,78-16,81]
MASLD	63	27	2,33* CI [1,37-3,96]
Chronic pancreatitis	32	5	6,40* CI [2,39-17,09]
Irritable bowel syndrome	52	11	4,73* CI [2,33-9,58]

In patients of Group 1, a number of cardiovascular diseases were identified that could contribute to a complicated course of COVID-19 (see Table 4.3.1). Thus, 49.0% of patients had underlying arterial hypertension, which was 4.1 times more frequent than in Group 2 (12.0%) (OR=4.08, CI [2.05-8.14]) ($p<0.05$). 31.0% of patients in Group 1 suffered from various forms of ischemic heart disease compared to 8.0% in Group 2, which was 3.9 times higher (OR=3.88, CI [1.69-8.84]) ($p<0.05$). The frequency of arrhythmias was nearly identical in both groups (7.0% and 5.0% in Groups 1 and 2, respectively), including extrasystolic arrhythmias and permanent atrial fibrillation.

In Group 1, acute myocarditis developed 6.8 times more often during SARS-CoV-2 infection compared with Group 2 (OR=6.80, CI [2.55-18.10]) ($p<0.05$). Signs of left-ventricular heart failure occurred 2.7 times more often in Group 1 (OR=2.67, CI [1.18-6.02]) ($p<0.05$). A nearly similar frequency of other rheumatologic diseases was observed in both groups (12.0% vs. 7.0%), including rheumatic heart disease, osteoarthritis of large joints, and the articular form of psoriasis. Additionally, in Group 1, chronic kidney disease stage I-II was identified 4.7 times more frequently (28.0% vs. 6.0%) (OR=4.67, CI [1.85-11.76]) ($p<0.05$), and it tended to progress during COVID-19, aggravating the course of pneumonia.

A higher frequency of acute reactive hepatitis was also recorded in Group 1 (41.0% vs. 6.0%) (OR=6.80, CI [2.78-16.81]) ($p<0.05$). Similarly, chronic pancreatitis in the acute phase was registered 6.4 times more often (32.0% vs. 5.0%) (OR=6.40, CI [2.39-17.09]) ($p<0.05$), as well as metabolic dysfunction-associated steatotic liver disease (MASLD) (OR=2.33, CI [1.37-3.96]) ($p<0.05$). During COVID-19, clinical manifestations of irritable bowel syndrome were observed in 52.0% of patients in Group 1 compared with 11.0% in Group 2 (OR=4.73, CI [2.33-9.57]) ($p<0.05$). Notably, in half of the patients, IBS symptoms with diarrheal syndrome persisted at hospital discharge.

At the same time, patients in Group 2 demonstrated a higher frequency of underlying pulmonary diseases compared with Group 1. The prevalence of bronchial asthma was twice as high in Group 2 (OR=2.0, CI [0.86-4.66]) ($p>0.05$). The frequency of COPD in Group 2 was three times higher than in Group 1 (OR=3.0, CI [1.29-6.99]) ($p<0.05$), indicating that pathogens causing viral-bacterial pneumonia can induce hypersensitivity and inflammatory swelling of the bronchial walls, leading to broncho-obstructive syndrome de novo, or trigger exacerbations of COPD and asthma. This was further aggravated by the significantly higher prevalence of tobacco smoking – 13.0% in Group 1 versus 31.0% in Group 2, i.e., 2.4 times more frequent (OR=2.38, CI [1.18-4.82]) ($p<0.05$), contributing to bronchopulmonary complications in Group 2.

Thus, the background somatic conditions contributing to a complicated course of COVID-19 in Group 1 included higher rates of overweight and obesity, hyper- and dyslipidemia, type 2 diabetes, arterial hypertension, ischemic heart disease, acute myocarditis, heart failure, CKD, MASLD, acute reactive hepatitis, pancreatitis, and irritable bowel syndrome. In Group 2, a higher prevalence of smoking, bronchial asthma, and COPD was recorded.

CHAPTER 5
ANEMIA IN CORONAVIRUS DISEASE: EPIDEMIOLOGICAL FEATURES, STRUCTURAL-PATHOGENETIC MECHANISMS AND CLINICAL SIGNIFICANCE

5.1. Age- and gender-related features of the prevalence of anemic syndrome in patients with coronavirus disease

According to data from large epidemiological studies, anemic syndrome is observed in 14-79% of patients with various internal diseases. In cases of combined course of coronavirus disease and anemia, the hemoglobin level in a significant proportion of patients may decrease to critical values (70-80 g/L), which markedly impairs tissue oxygenation.

In anemia, along with hypoxic disturbances, pronounced secondary metabolic disorders develop, leading to dysfunction of physiologically active substances and intensifying endogenous metabolic intoxication. The severity of this syndrome directly depends on the degree of anemia and the level of hypoxia, which is particularly important in the context of coronavirus disease, as COVID-19 itself induces systemic inflammation, oxidative stress, and microcirculatory dysfunction.

The aim of our research was to determine the prevalence of anemic conditions (AC) in patients with verified coronavirus disease who were hospitalized due to the underlying illness. To achieve this objective, a retrospective analysis of 870 medical records of patients who underwent inpatient treatment in the therapeutic departments of the Chernivtsi Regional War Veterans Hospital (Chernivtsi) during 2020-2021 was conducted. Inclusion in the study was based on a confirmed diagnosis of COVID-19. The mean age of the examined patients was 51.5±3.24 years, with an age range from 42 to 68 years. Anemia was defined as a hemoglobin level below 130 g/L in men and 120 g/L in women, according to WHO recommendations.

The age distribution of the patients is presented in Fig. 5.1.1. Medical records of 152 middle-aged patients (42-59 years) – 17.47%, and 718 elderly patients (60-68 years) – 82.53% were analyzed. In terms of gender, men predominated over women (62.07% vs. 37.93%, respectively).

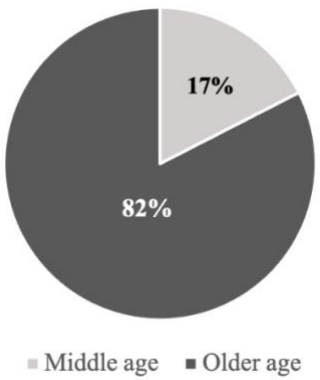


Fig. 5.1.1. Age distribution of patients with coronavirus disease, %

The summarized data on the distribution of patients by age and gender are presented in Table 5.1.1. Among all examined patients, anemia syndrome (AS) was identified in 32.07% (279 cases), which is consistent with the literature data. Analysis of the distribution of anemia among patients hospitalized with COVID-19 revealed age- and gender-specific features in the frequency and severity of concomitant anemia.

Among all patients with concurrent COVID-19 and AS, a mild degree of anemia (Hb 90-120 g/L in women and 90-130 g/L in men) was detected in 127 cases (45.5%), moderate anemia (Hb 70-89 g/L) in 91 cases (32.6%), and severe anemia (Hb below 70 g/L) in 61 cases (21.9%) (Fig. 5.1.2).

Table 5.1.1

Distribution of patients with coronavirus disease by sex and age

	Middle age (42-59 years old)		**Older age (60-68 years old)**	
	males	***females***	***males***	***females***
Number	115	37	425	293
%	13,22	4,25	48,85	33,68

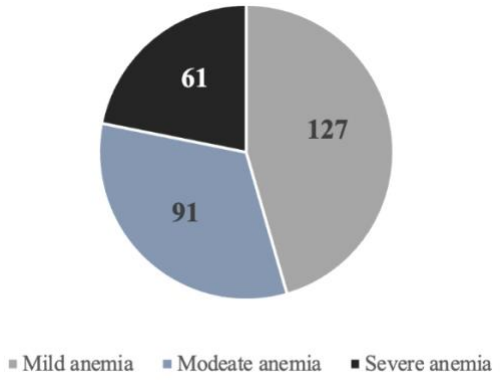


Fig. 5.1.2. Severity of comorbid anemia in patients with coronavirus disease

The prevalence of mild and moderate degrees of comorbid anemia in the analyzed cases may indicate timely diagnosis and effective correction of reduced hemoglobin levels in this category of patients, which prevents its progression to severe anemia. Severe forms of anemia occur less frequently; however, they may have a significant impact on the course of COVID-19, especially in patients with severe inflammation and comorbid chronic diseases.

Analysis of the distribution of anemia severity among patients of different age groups revealed certain patterns that may have important clinical implications. Among middle-aged patients with coronavirus disease and concomitant anemia (140 cases), mild anemia predominated and was diagnosed in 67 patients (47.9%). Moderate anemia was identified in 40 cases (28.6%), whereas severe hemoglobin reduction was observed in 33 patients (23.6%).

In the elderly group (139 cases), the frequency of mild anemia was slightly lower at 60 cases (43.2%), while the frequency of COVID-19 complicated by moderate anemia increased to 51 cases (36.7%). Severe anemia was recorded in 28 cases (20.1%) (Fig. 5.1.3).

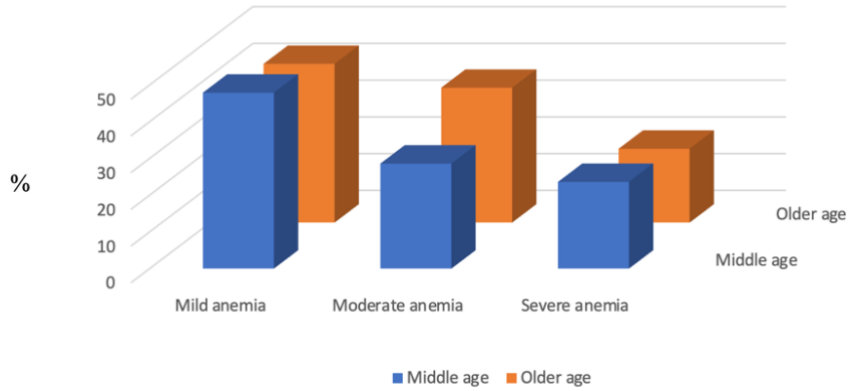


Figure 5.1.3. Severity of comorbid anemia in patients with coronavirus disease by age group

The obtained data indicate that in middle-aged patients anemia more often presents in a mild form, which may be associated with relatively preserved hematopoietic reserve capacity, adequate erythropoietic activity, and a lower prevalence of comorbid conditions. In contrast, among elderly patients there is a clear trend toward a higher number of cases with moderate and severe anemia. This may be explained by age-related alterations in iron metabolism, impaired mechanisms of iron absorption and utilization, reduced erythropoietin activity, as well as the presence of chronic comorbid diseases that contribute to the progression of anemia severity.

An important aspect, in our opinion, is that despite the overall tendency toward more frequent moderate and severe forms of anemia in older adults with COVID-19, their proportion remains relatively low. This may reflect effective clinical monitoring, early detection of declining hemoglobin levels, and timely correction of comorbid anemia through preventive measures, hemoglobin control, and adequate management of underlying chronic conditions.

Analysis of the severity distribution of comorbid anemia by gender among patients with COVID-19 revealed the following patterns. The total number of anemia cases among men was 148, whereas among women 131 cases were recorded. In men, mild anemia was diagnosed in 67 patients (45.3%), moderate anemia in 45 cases (30.4%), and severe anemia in 36 patients (24.3%). A similar analysis among women showed that mild anemia occurred in 60 cases (45.8%), moderate in 46 patients (35.1%), and severe anemia in 25 women (19.1%) (Fig. 5.1.4).

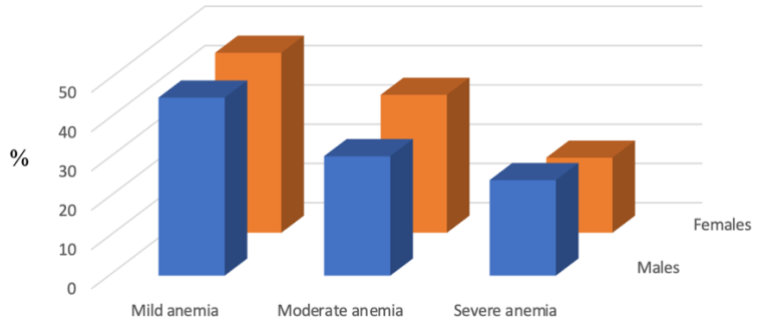


Figure 5.1.4. Severity of comorbid anemia in patients with coronavirus disease: gender distribution

The obtained results indicate an almost identical prevalence of mild anemia among men and women, which may be explained by the influence of shared risk factors characteristic of the combined course of anemia and COVID-19 namely chronic inflammation, impaired iron metabolism, and oxidative stress. At the same time, moderate anemia was more frequently observed in women, likely due to their higher physiological iron requirements related to regular blood loss, pregnancy, and lactation. Women also seek medical care more often for preventive check-ups, which facilitates early detection of both anemia and chronic internal diseases associated with reduced hemoglobin levels. This may partly explain the lower frequency of severe anemia among females.

In contrast, men in the analyzed cohort of hospitalized COVID-19 patients demonstrated a higher frequency of severe anemia (24.3% compared with 19.1% in women), which may result from several contributing factors. First, men are known to have a higher risk of severe COVID-19, which is often accompanied by more profound impairment of hematopoiesis. Second, the prevalence of comorbid conditions such as cardiovascular diseases, chronic kidney disease, liver pathology, and gastrointestinal disorders is generally higher among men, contributing to the development of comorbid anemia. Moreover, oxidative stress, one of the key mechanisms of COVID-19 pathogenesis, tends to be more aggressive in males, potentially leading to deeper depletion of iron stores and erythropoietic capacity.

Thus, the identified gender-specific differences in anemia severity among COVID-19 patients may be attributed to both physiological and pathological mechanisms. In women, COVID-19 more often resulted in comorbid anemia of moderate severity, likely due to increased iron requirements and greater attention to preventive healthcare. In men, severe anemia was more prevalent, which may be associated with delayed diagnosis, a higher burden of comorbid chronic diseases, and a greater propensity for severe COVID-19 in male patients.

Analysis of the obtained data demonstrated that the presence of anemia in patients with COVID-19 may be a significant factor increasing the risk of developing pneumonia. In particular, among the 279 patients with anemia diagnosed according to

WHO criteria, pulmonary involvement in the form of viral-bacterial pneumonia was registered in 201 cases, which corresponds to 72% of this group (Fig. 5.1.5). At the same time, among patients without anemia (n=591), the frequency of pneumonia was only 38% (224 cases). Thus, the comparative analysis shows that the incidence of pneumonia among individuals with anemia was almost twice as high compared to patients with normal hemoglobin levels.

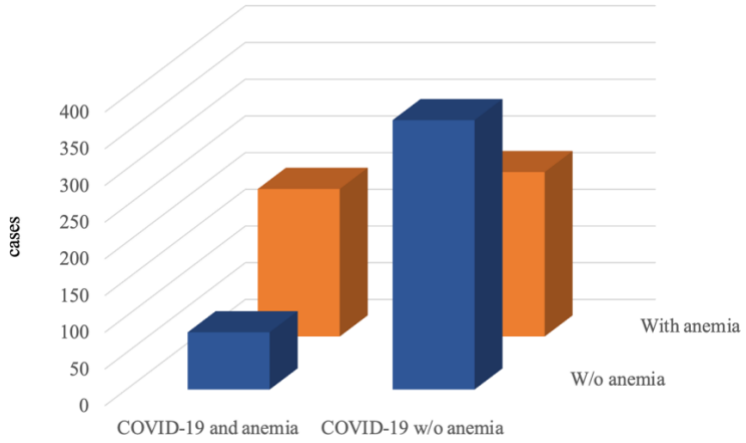


Figure 5.1.5. Complication of COVID-19 infection by pneumonia depending on the presence of comorbid anemia

The obtained results allow us to assume that anemia may be an independent predictor of an unfavourable course of coronavirus disease, particularly regarding the development of severe viral-bacterial pneumonia. This may be explained by the fact that a decrease in hemoglobin levels is accompanied by impaired tissue oxygenation, which in turn leads to the progression of hypoxic changes in the pulmonary parenchyma. Under conditions of acute viral inflammation, this may, in our opinion, contribute to more aggressive damage to the alveolar apparatus, the development of diffuse alveolar injury, and the formation of respiratory failure.

Thus, among patients with a verified diagnosis of coronavirus disease, comorbid anemia was identified in 32.07% of cases, which indicates a high prevalence of this complication in the infectious process against a background of somatic pathology. Among the analyzed medical records of patients with COVID-19, mild (45.5%) and moderate (32.6%) anemia predominated, whereas severe hemoglobin reduction was observed in 21.9% of cases.

In patients with COVID-19 of middle age, mild anemia was more frequently registered (47.9%), while in elderly patients a higher frequency of moderate (36.7%) and severe (20.1%) anemia was noted, indicating a significant influence of age-related hematopoietic features on the frequency and severity of the anemic syndrome. Moderate anemia was more commonly detected in women (35.1%), whereas severe anemia predominated in men (24.3%), which is likely associated with a higher frequency of severe COVID-19 and the presence of comorbid pathology in men, as well as with physiological characteristics of iron metabolism in women.

A clear relationship was established between the presence of anemia and the frequency of viral-bacterial pneumonia in patients with COVID-19: in anemic patients this complication occurred in 72% of cases, whereas among individuals with normal hemoglobin levels it was observed in only 38%. This finding allows anemia to be considered a possible predictor of an unfavourable course of COVID-19.

5.2. Structure and origin of the anemic syndrome in patients with coronavirus disease

Assessment of the possible origin of anemia in patients with COVID-19 is a key step in forming an individualized management strategy and determining the disease prognosis. Given that the anemic syndrome in coronavirus disease may be caused by iron deficiency, chronic inflammation, concomitant bone marrow involvement, or hemolysis, identifying its pathogenetic mechanisms allows the selection of the most effective therapeutic approaches.

In particular, iron supplementation is appropriate in iron-deficiency anemia, whereas in anemia of chronic inflammation it is necessary to correct systemic inflammatory activity and oxidative stress. Furthermore, accurate differential diagnosis enables timely detection of hidden comorbid conditions that may complicate the course of COVID-19 and reduce treatment effectiveness. Therefore, determining the pathogenetic variant of anemia contributes to optimizing therapeutic approaches, improving treatment efficacy, and enhancing the prognosis of patients with concomitant COVID-19 and anemia.

A retrospective analysis of the medical records of patients with concurrent COVID-19 and anemia showed that the clinical presentation of the comorbid anemic syndrome was characterized by a constellation of symptoms resulting from insufficient tissue oxygenation, metabolic disturbances, and compensatory cardiovascular responses to anemic hypoxia.

The main complaints included general weakness, rapid fatigability, dizziness, and exertional dyspnea, which likely reflected reduced blood oxygen-carrying capacity and impaired oxygen delivery to organs and tissues. Patients often noted palpitations, irregular heartbeat, and a tendency toward arterial hypotension, which can be explained by a compensatory increase in cardiac output in response to hypoxia. In some cases, medical records documented pale skin, headache, and reduced working capacity – manifestations consistent with systemic tissue hypoxia and circulatory disturbances.

No complaints or objective findings suggesting hemolytic (frequent infections in history, jaundice, splenomegaly, reticulocytosis, microspherocytosis, etc.) or aplastic anemia were identified in the analyzed documentation. When reviewing patient complaints upon admission and the results of physical examination, we also paid attention to signs that could support an iron-deficiency or megaloblastic origin of the anemia (Table 5.2.1).

Table 5.2.1

General characteristics of complaints and objective findings typical for iron-deficiency and vitamin B_{12}-deficiency anemias in patients with coronavirus disease

Clinical findings	COVID-19 and anemia (n=279)	
	Number of patients	%
Brittle nails	3	1,07%
Koilonychia	-	0%
Hair loss	5	1,79%
Dysgeusia	-	0%
Angular cheilitis	2	0,72%
Dysosmia	-	0%
“Blue sclerae”	-	0%
Tongue soreness	2	0,72%
Dysphagia	-	0%
“Cotton wool” sensation in the legs	1	0,36%
Paraesthesia in the extremities	9	3,22%
Jaundice	-	0%
Ataxic gait	7	2,51%
Hunter’s glossitis	-	0%

The obtained results indicate the presence of features of the so-called “general anemic syndrome” (circulatory-hypoxic syndrome) in the clinical presentation. In contrast, the specific manifestations of the most common clinical and pathogenetic variants of anemia (sideropenic syndrome, funicular myelosis, gastroenterological syndrome) were sporadic, and in many cases may have been caused by non-hematological factors (hypovitaminosis, trace element deficiencies, dyscirculatory ischemic encephalopathy, physiological aging, etc.).

While comparing the degree of erythrocyte hemoglobin saturation in the analyzed inpatient medical records of patients with coronavirus disease, hyperchromic anemia (color index >1.05) was identified in 8 patients (2.87%), hypochromic anemia (color index <0.86) in 35 patients (12.54%). In the majority of cases, anemia in coronavirus disease was normochromic – 236 patients (84.59%) (Fig. 5.2.1).

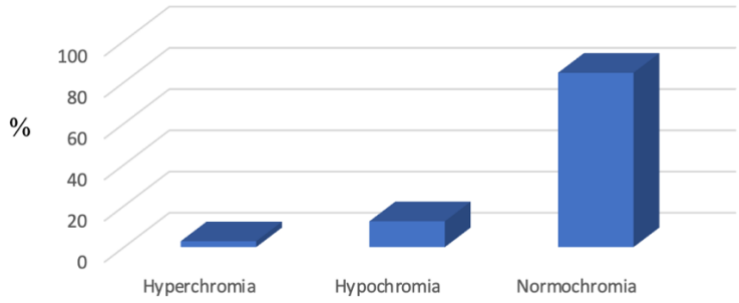


Fig. 5.2.1. Type of anemia in patients with coronavirus disease

To determine the morphological characteristics of the anemic syndrome in patients with COVID-19, the mean corpuscular volume (MCV) was calculated. Mild

macrocytosis (MCV 95-108 fL) was identified only in isolated cases – 5 patients (1.79%). Microcytosis (MCV <80 fL) was observed in 41 patients (14.69%), while normocytosis was recorded in 233 patients (83.52%) (Fig. 5.2.2).

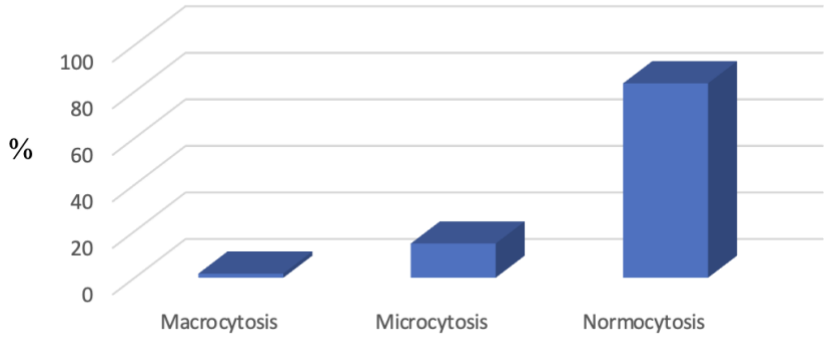


Fig. 5.2.2. Morphological characteristics of the anemic syndrome in patients with coronavirus disease

The obtained results indicate that in most hospitalized patients with coronavirus disease, the anemic syndrome was normochromic and normocytic, which points to its predominantly inflammatory origin. Given this type of anemia, the clinical and pathogenetic variants of anemia accompanied by hyperchromia and macrocytosis, primarily megaloblastic anemias (vitamin B_{12}- and folate-deficiency anemias), can be excluded in the examined group.

Normal values of the mean corpuscular volume and hemoglobin content per erythrocyte, together with a reduced total hemoglobin concentration, are characteristic of anemia of chronic disease, which develops as a result of prolonged systemic inflammation. The main mechanisms of this type of anemia include impaired iron metabolism, an inadequate erythropoietin response to hypoxia, and suppression of erythropoiesis under the influence of pro-inflammatory cytokines, particularly interleukin-6. COVID-19 is known to be associated with hypercytokinemia and systemic inflammation, which lead to blocked mobilization of iron from storage sites, the development of functional iron deficiency, and impaired erythrocyte production in the bone marrow. The absence of pronounced microcytosis or macrocytosis indicates that the principal pathogenetic mechanism of anemia in these patients is inflammatory suppression of erythropoiesis rather than iron or vitamin B_{12} deficiency.

Among all reviewed medical records, COVID-19 combined with anemia most frequently co-occurred with chronic obstructive pulmonary disease (78.85%); 27.96% of patients had a history of peptic ulcer disease (stomach and duodenum); 4.31% suffered from malignancies of various localizations; and in 20.07% of cases, anemia occurred in isolation.

Parameters of iron metabolism were also analyzed in patients with COVID-19 and anemia depending on the severity of the latter. No significant differences were found between the studied groups: in all patients, plasma iron levels were reduced and did not differ substantially depending on the degree of anemic syndrome ($p>0.05$) (Fig. 5.2.3).

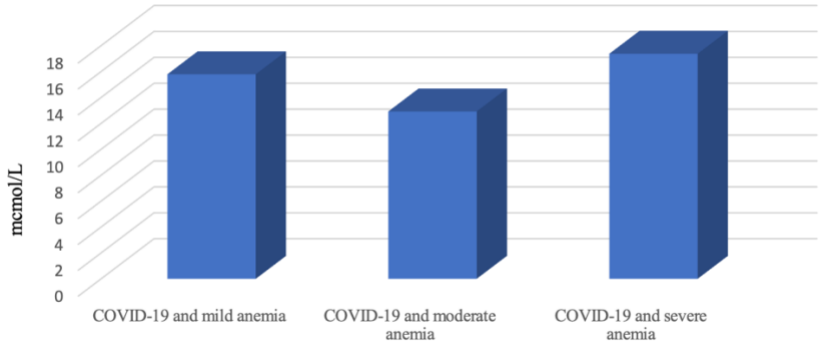


Fig. 5.2.3. Serum iron levels in patients with coronavirus disease and comorbid anemia of different severity

The indicator of total iron-binding capacity (TIBC) of blood serum (Fig. 5.2.4) in patients with coronavirus disease and mild anemia was 35.78±1.29 μmol/L, in patients with COVID-19 and moderate anemia – 34.99±2.37 μmol/L, and in those with COVID-19 combined with severe anemia – 34.73±2.54 μmol/L ($p>0.05$ in all cases).

These values were below normal reference ranges, which allowed us to exclude a probable iron-deficiency origin of the comorbid anemic syndrome.

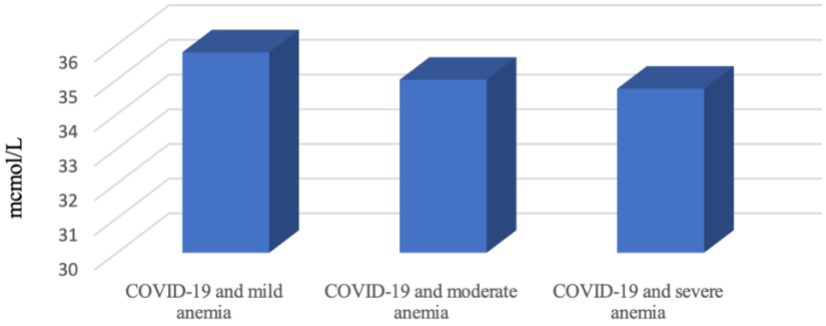


Fig. 5.2.4. Total iron-binding capacity of blood serum in patients with coronavirus disease and comorbid anemia of different severity

Thus, in the overwhelming majority of analyzed cases of combined coronavirus disease and anemia, the comorbid anemic syndrome corresponded to the clinical and pathogenetic variant of anemia of chronic disease.

Therefore, analysis of the clinical presentation of the comorbid anemic syndrome in patients with COVID-19 demonstrated the predominance of non-specific symptoms of the general circulatory-hypoxic type of anemia. The obtained results confirm that in most hospitalized patients with COVID-19, the comorbid anemia is inflammatory in nature and corresponds to the clinical and hematological characteristics of anemia of chronic disease.

5.3. Pathogenetic markers of anemia of chronic inflammation in patients with COVID-19 and their prognostic significance

Anemia accompanying the course of coronavirus disease is an important clinical and laboratory marker that can substantially influence disease severity, the need for respiratory support, and the duration of hospitalization. Establishing the pathogenetic type of anemia is crucial for selecting an appropriate therapeutic strategy, since the mechanisms underlying its development in COVID-19 are heterogeneous. Among them, a particularly important role belongs to anemia of chronic inflammation, which develops due to activation of pro-inflammatory cytokines especially interleukin-6 that suppress erythropoiesis and disrupt iron metabolism.

One of the key laboratory markers reflecting a systemic inflammatory response is ferritin, an iron-storage protein whose level is often markedly elevated in COVID-19. Increased ferritin concentration in the absence of signs of absolute iron deficiency indicates the development of functional iron deficiency, characteristic of anemia of chronic disease. In such cases, traditional iron-replacement therapy is ineffective, and the primary therapeutic approach focuses on controlling systemic inflammation.

Another parameter with potential prognostic significance is procalcitonin, whose level rises proportionally to the severity of anemia and the intensity of the inflammatory process. Elevated procalcitonin may also indicate a risk of secondary bacterial infection. Comprehensive assessment of ferritin and procalcitonin levels allows not only evaluation of the type of anemia but also prediction of its impact on the clinical course of COVID-19.

This subsection presents the results of an analysis of biochemical markers of inflammation and iron metabolism in patients with combined coronavirus disease and anemic syndrome, as well as their relationship with clinical features of the primary illness.

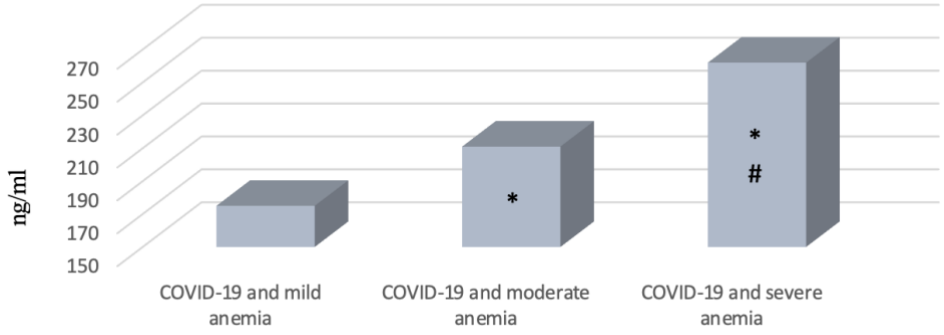


Fig. 5.3.1. Blood ferritin levels in patients with coronavirus disease and comorbid anemia of different severity

Note: * – statistically significant difference compared with patients with COVID-19 and mild anemia ($p<0.05$); # – statistically significant difference compared with patients with COVID-19 and moderate anemia ($p<0.05$).

Among the 279 inpatient medical records analyzed, ferritin levels were measured in only 57 cases (20.43%) in private laboratories in Chernivtsi. Analysis of the obtained data revealed an elevated ferritin level in nearly all examined cases (Fig. 5.3.1), which showed an inverse correlation with hemoglobin level, $p<0.05$ (Fig. 5.3.2).

The obtained data indicate a pathogenetic mechanism typical of anemia of chronic inflammation, in which functional iron deficiency develops despite adequate or elevated iron stores, due to impaired iron utilization. The increase in ferritin levels in this cohort reflects the systemic inflammatory response characteristic of COVID-19, associated with activation of hepcidin, the key regulator of iron homeostasis. Under the influence of pro-inflammatory cytokines, hepcidin inhibits the release of iron from storage sites and its transport to erythropoietic cells, leading to ineffective erythropoiesis and a reduction in hemoglobin levels. This imbalance between ferritin and hemoglobin does not indicate absolute iron deficiency but rather functional iron unavailability, which does not respond to standard iron supplementation. Taken together, the identified changes confirm the immuno-inflammatory origin of anemia in patients with COVID-19 and emphasize the need for a differentiated therapeutic approach.

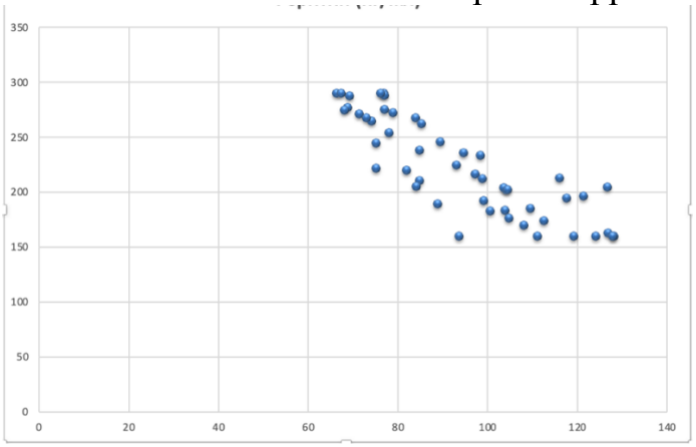


Fig. 5.3.2. Inverse correlation between hemoglobin level (g/L) and ferritin level (ng/mL) in patients with comorbid anemia and coronavirus disease

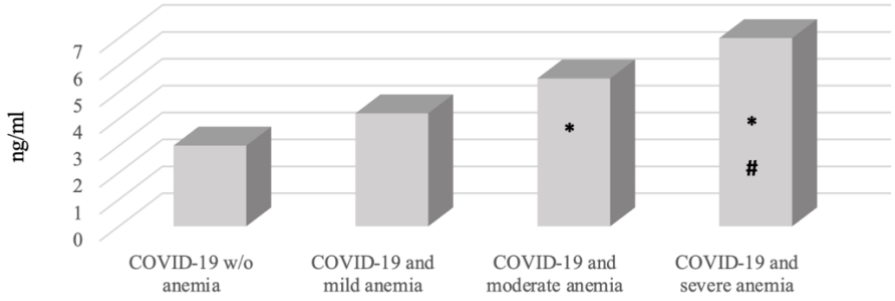


Figure 5.3.3. Procalcitonin levels in patients with coronavirus disease depending on the severity of comorbid anemia

Note: * — statistically significant difference compared with patients with COVID-19 without anemia ($p<0.05$); # – statistically significant difference compared with patients with COVID-19 and moderate anemia ($p<0.05$).

The analysis of 89 medical records of patients with concurrent anemia and coronavirus disease demonstrated a statistically significant ($p<0,05$) association between procalcitonin levels and the severity of anemia (Fig. 5.3.3). It was established that the mean procalcitonin level in patients with mild anemia was 4.2±0.5 ng/mL, in those with moderate anemia – 5.5±0.7 ng/mL, and in patients with severe anemia – 7.0±0.5 ng/mL. For comparison, in patients with COVID-19 without anemia, the mean procalcitonin level was 3.0±0.4 ng/mL, which is significantly lower than in all anemia groups ($p<0.05$).

The identified differences indicate a progressive increase in procalcitonin concentration with increasing severity of anemia, reflecting the relationship between the degree of hypoxia and the intensity of the inflammatory response in these patients.

The increase in procalcitonin levels in patients with anemia on the background of COVID-19 can be explained by several key pathogenetic mechanisms. First, more severe anemia is accompanied by a greater degree of hypoxic stress, which promotes the activation of proinflammatory mediators, particularly interleukin-6 (IL-6), the main inducer of procalcitonin synthesis. Second, patients with more pronounced hemoglobin deficiency more frequently develop secondary bacterial complications, which leads to an additional increase in procalcitonin levels, since this marker is specific for bacterial infection. Third, anemia in the setting of COVID-19 is associated with marked microcirculatory disturbances that contribute to endothelial dysfunction, increased vascular permeability, and the release of proinflammatory proteins into the bloodstream.

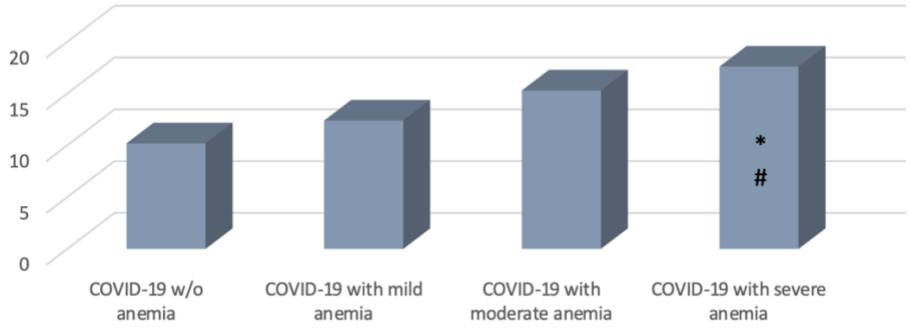


Figure 5.3.4. Average duration of in-hospital treatment depending on the severity of comorbid anemia

Note: * – statistically significant difference compared to patients with COVID-19 without anemia ($p<0.05$); # – statistically significant difference compared to patients with COVID-19 and mild anemia ($p<0.05$).

Analysis of the obtained results indicates that patients with COVID-19 without anemia have lower procalcitonin levels compared with those with anemia, which confirms the role of the anemic syndrome as an additional factor in the hyperinflammatory response. At the same time, even in severe anemia, procalcitonin levels did not exceed 7.5 ng/mL, which suggests the absence of a secondary bacterial component and instead may indicate activation of secondary systemic inflammation.

The identified pattern underscores the need for comprehensive monitoring of patients with COVID-19 and anemia, including regular assessment of procalcitonin levels as a potential indicator of the risk of secondary bacterial complications. This also confirms the need for a personalized approach to the management of such patients, which should include not only hemoglobin correction but also active strategies for controlling the inflammatory response.

Among patients with coronavirus disease and anemia, the average duration of in-hospital treatment was 14.8±2.3 days, which was statistically significantly longer than in patients with COVID-19 without anemia (10.2±1.9 days, $p<0.05$). In patients with COVID-19 and mild anemia, the mean duration of hospitalization was 12.4±1.6 days. The length of inpatient treatment for patients with moderate anemia was 15.3±2.1 days, and in cases of severe anemia this indicator reached 17.6±2.9 days (Fig. 5.3.4). These findings indicate a substantial impact of hemoglobin deficiency on the clinical course of COVID-19.

The established patterns demonstrate that anemia of varying severity worsens the course of COVID-19 and leads to prolongation of hospital stay. In our view, these findings can be explained as follows. It is known that anemia reduces oxygen transport to tissues and causes hemic hypoxia, which under conditions of SARS-CoV-2 induced respiratory system damage, further exacerbates existing tissue hypoxia. In patients with COVID-19 and comorbid anemia, the risk of developing respiratory failure increases, thereby elevating the need for additional respiratory support. These circumstances significantly complicate the course of the disease, delay recovery, and necessitate extended clinical monitoring in the hospital.

Thus, in the combined course of COVID-19 and anemia, a significant increase in ferritin levels was identified, which inversely correlated with hemoglobin concentration ($p<0.05$), indicating functional iron deficiency against the background of systemic inflammatory response. Elevated procalcitonin levels in patients with COVID-19 and anemia correlated with anemia severity, demonstrating a direct relationship between the extent of anemic hypoxia and the intensity of systemic inflammation. It was established that the presence of comorbid anemia is associated with a significant prolongation of hospital stay (14.8±2.3 days vs. 10.2±1.9 days in patients without anemia, $p<0.05$), indicating its negative impact on the clinical course of COVID-19.

CHAPTER 6
ANALYSIS AND DISCUSSION OF THE OBTAINED RESULTS

A significant increase in the incidence of CAP associated with COVID-19 in the last decade has contributed to increased scientific attention to this topic and to the identification of clinical features of its course. The relevance of the topic lies in the considerable prevalence of COVID-19 worldwide and in Ukraine since 2020 and the high mortality rate from the complicated course of the disease. The main clinical manifestation of COVID-19 involving the lower respiratory tract is viral CAP or early viral-bacterial pneumonia. Currently, a decrease in the incidence of CAP in the population is observed, its association with SARS-CoV-2 infection, which occurs during (viral) or immediately after the acute COVID-19 illness (primary viral-bacterial or secondary bacterial pneumonia), and the high frequency of severe CAP on the background of comorbid conditions such as obesity, diabetes mellitus, heart failure, CKD and liver diseases.

The epidemic of COVID-19 caused by SARS-CoV-2 began in December 2019 in Wuhan, Hubei Province, China, and was declared a pandemic by WHO on March 11, 2020. On December 30, 2019, a report on the emergence of "pneumonia of unknown origin" was published by the Medical Administration of China and the Medical Administration of the Wuhan Municipal Health Committee. On January 9, 2020, WHO confirmed that a new coronavirus had been isolated from a hospitalized patient. On the same day, the European Centre for Disease Prevention and Control published its first risk assessment.

During the pandemic, 704.75 million people worldwide became ill. More than 7.0 million died. According to the Ministry of Health and the National Security and Defense Council, as of April 13, 2024, 5,557,995 cases of SARS-CoV-2 infection (13.5%) have been confirmed in Ukraine, of which 112,418 people died (2.0%), and 5,445,577 recovered (98.0%). At the peak of the epidemic, the overall mortality from COVID-19 was around 2%, and 5-20% of patients with COVID-19 required hospitalization, among whom 10-30% required intensive care, creating a significant burden on healthcare systems. In 35-40% of individuals with COVID-19, mild CAP develops, and in 15-28% moderate CAP, while in 10-15% severe CAP may develop, requiring intensive care with oxygen support, and in 5% extremely severe CAP occurs with complications such as respiratory failure, ARDS (non-cardiogenic pulmonary edema), sepsis and septic shock, thromboembolism and/or multiorgan failure involving the kidneys, liver, and myocardium.

In May 2023, WHO announced that COVID-19 was no longer a Public Health Emergency of International Concern, but acknowledged that the epidemic was not over. Therefore, early diagnosis of CAP occurring on the background of COVID-19, studying the features of its clinical course with prediction of a severe, complicated course of CAP and preventing these complications is an important task in public health and determines the relevance of scientific research in this direction. At the same time, the literature review, published studies and articles on the features of the clinical course of CAP on

the background of COVID-19 compared with other community-acquired pneumonias, reveals a rather limited number.

Analysis of CAP morbidity showed that women were more often treated for CAP-S (62.0%) compared to 38.0% of men ($p<0.05$). Meanwhile, in patients with CAP-VB, the ratio women/men was 53.0% vs 47.0% ($p>0.05$). According to age distribution, CAP-S was more common in individuals aged 51-75 years (49.0%) (OR=1.96 CI [1.12-3.42]) ($p<0.05$), while CAP-VB was more common in young individuals <50 years (51.0%) (OR=1.89 CI [1.09-3.25]) ($p<0.05$). The age category >75 years had equal incidence of CAP-S and CAP-VB (OR=1.0 CI [0.53-1.88]) ($p>0.05$). These data are consistent with the findings of several researchers indicating a similar trend.

Analysis of symptom frequency in CAP demonstrated statistically significant differences according to the following indicators: severe chest pain during breathing and coughing occurred 2.0 times more often in CAP-S compared to CAP-VB (OR=2.0 CI [1.26-3.18]) ($p<0.05$); fever was 1.7 times more frequent (OR=1.72 CI [1.12-2.63]) ($p<0.05$). Anosmia occurred 5.6 times more often in CAP-S compared to CAP-VB (OR=5.64 CI [2.80-11.33]) ($p<0.05$). Cough occurred with equal frequency in CAP-S and CAP-VB (OR=1.11 CI [0.73-1.66]) ($p>0.05$).

The frequency of dyspnea increasing in intensity was 1.7 times higher in CAP-S compared to CAP-VB (OR=1.76 CI [1.12-2.78]) ($p<0.05$); myalgia occurred 4.9 times more often (OR=4.93 CI [2.65-9.17]) ($p<0.05$). Marked general weakness with subsequent prolonged asthenia was recorded 3.6 times more often in CAP-S than in CAP-VB (OR=3.63 CI [2.18-6.03]) ($p<0.05$). Severe headache at disease onset occurred 2.2 times more often in CAP-S compared to CAP-VB (OR=2.19 CI [1.28-3.72]) ($p<0.05$); short episodes of loss of consciousness were observed 9.3 times more often in CAP-S (OR=9.33 CI [2.75-31.69]) ($p<0.05$); severe sore throat with odynophagia occurred 26.0 times more often in CAP-S (OR=26.0 CI [3.46-195.30]) ($p<0.05$); nausea occurred 2.2 times more often in CAP-S (OR=2.19 CI [1.28-3.72]) ($p<0.05$); diarrhea occurred 8.6 times more often in CAP-S than in CAP-VB (OR=8.6 CI [3.27-22.61]) ($p<0.05$).

Analyzing objective status and laboratory indicators, a statistically significant difference was found for the following parameters: a larger number of patients with CAP-S compared to CAP-VB had elevated body temperature above 38.5°C (OR=2.38 CI [1.44-3.91]) ($p<0.05$); heart rate above 90/min (OR=2.6 CI [1.57-4.30]) ($p<0.05$); respiratory rate above 25/min (OR=2.86 CI [1.64-5.01]) ($p<0.05$). In patients with CAP-S compared to CAP-VB, a higher frequency of reduced oxygen saturation of 90-92% was recorded 1.7 times higher (OR=1.73 CI [1.11-2.71]) ($p<0.05$).

These clinical features can be explained by the characteristics of viral spread throughout the respiratory tract, involving both upper and lower airways, reflecting the cytopathogenic effect of the coronavirus on the epithelium of the oral and nasopharynx, the trachea and bronchi, and most importantly, the pronounced effect of SARS-CoV-2 on type II alveolar epithelial cells, with inhibition of pulmonary surfactant secretion.

Analysis of the frequency of detection of clinical blood test parameters in patients with pneumonia associated with COVID-19 and viral-bacterial pneumonia indicates a

significant damaging effect of SARS-CoV-2 on leukocytes, lymphocytes, and platelets. Thus, in 65.0% of patients with COVID-19-associated pneumonia, leukopenia below 4.0×10^9/L was detected, compared with 32.0% in patients with viral-bacterial pneumonia (OR=2.03, CI [1.23-3.37]) ($p<0.05$). At the same time, 87.0% of patients with COVID-19-associated pneumonia were found to have lymphopenia of varying severity, compared with 27.0% in the viral-bacterial pneumonia group (OR=3.22, CI [1.93-5.38]) ($p<0.05$). In COVID-19-associated pneumonia, thrombocytopenia was also detected in 69.0% of patients, compared with 31.0% in those with viral-bacterial pneumonia (OR=2.23, CI [1.34-3.69]) ($p<0.05$).

Analysis of biochemical indicators reflecting the intensity of inflammation demonstrates a higher frequency of hyperfibrinogenemia (OR=2.66, CI [1.62-4.34]) in COVID-19-associated pneumonia ($p<0.05$), as well as hyperferritinemia (OR=3.72, CI [2.06-6.71]) ($p<0.05$).

Patients with COVID-19-associated pneumonia had a 2.6-fold higher frequency of elevated C-reactive protein above 20 mg/L (OR=2.57, CI [2.76-52.13]) ($p<0.05$), as well as a 1.9-fold higher frequency of increased ESR above 15 mm/h (OR=1.93, CI [1.13-3.29]) ($p<0.05$). These data indicate that COVID-19 triggers a systemic inflammatory response of considerable intensity, significantly exceeding the inflammation seen in viral-bacterial pneumonia, which is consistent with numerous published studies.

Analysis of indicators of pigment metabolism demonstrated a significant increase in total bilirubin content in patients of group 1 – 1.9-fold higher, and in group 2 – 1.2-fold higher ($p<0.05$) compared with the control group, which indicates the hepatotropic properties of SARS-CoV-2 with the ability to damage hepatocytes. Analysis of the fraction ratios of total bilirubin indicates an increase in the conjugated fraction in group 1 by 1.7-fold ($p<0.05$), and the unconjugated fraction by 2.0-fold ($p<0.05$). Thus, abnormalities of bilirubin metabolism in patients with COVID-19-associated pneumonia indicate pathogenetic hepatotropism of the virus, contributing to the severity of the patient's condition.

ALT activity in group 1 exceeded the control by 3.5-fold ($p<0.05$), and AST activity by 2.9-fold ($p<0.05$), indicating hepatocellular cytolysis in patients with COVID-19-associated pneumonia and suggesting reactive hepatitis of moderate activity. In group 1, a 1.2-fold decrease in the De Ritis ratio (AST/ALT) was observed ($p<0.05$), indicating the presence of hepatitis of viral origin. In group 2, the activity of the cytolytic syndrome was significantly lower compared with group 1. ALT activity in group 2 exceeded the control by 1.8-fold ($p<0.05$), and AST activity by 1.4-fold ($p<0.05$), and both significantly differed from the values observed in group 1 ($p<0.05$). Under these conditions, the De Ritis ratio (AST/ALT) was 1.3-fold lower than in the control ($p<0.05$), indicating the development of inflammatory liver disease presumably of viral origin.

The presence of mesenchymal inflammatory syndrome was indicated by an increased thymol turbidity test in both comparison groups: in group 1 it exceeded the control by 1.9-fold, and in group 2 by 1.3-fold ($p<0.05$). Blood fibrinogen level in group

1 was significantly higher than in the control – 2.3-fold higher ($p<0.05$), and ferritin 8.9-fold higher versus a 4.1-fold increase in group 2. CRP level exceeded the control by 24.9-fold in group 1 compared to 5.7-fold in group 2. Patients with COVID-19-associated pneumonia were found to have cholestasis syndrome. Increased ALP activity by 1.3-fold ($p<0.05$) compared to the control, as well as parallel elevation of γ-GT activity – also 1.3-fold higher ($p<0.05$), indicates the presence of a cholestatic syndrome.

Thus, COVID-19 complicated by pneumonia was accompanied by significant liver parenchymal damage with the development of cytolytic, cholestatic, and mesenchymal-inflammatory syndromes of moderate activity, which is consistent with the results of numerous studies.

At the same time, an increase in blood creatinine levels was found in group 1 – 2.0-fold ($p<0.05$) compared with a 1.2-fold increase in group 2 ($p<0.05$), which indicates the nephrotropic activity of SARS-CoV-2. An increase in blood urea concentration was also established in both groups of patients: in group 1 a 2.4-fold increase ($p<0.05$) versus a 1.5-fold increase in group 2 ($p<0.05$). Thus, coronavirus infection complicated by pneumonia was accompanied by significant injury to the renal parenchyma, with the development in some cases of acute kidney injury, and in others – progression of comorbid chronic kidney disease against the background of COVID-19. A number of authors confirm the nephrotropic effect of SARS-CoV-2.

As a result of radiological examinations of the chest organs in patients with COVID-19-associated pneumonia, bilateral localization of pneumonia was more frequently observed – 66.0% versus 34.5% in viral-bacterial pneumonia, which was 1.9 times more common in COVID-19-associated pneumonia (OR=1.94, CI [1.18-3.19]) ($p<0.05$). In addition, pleural inflammatory reactions were detected 6.3 times more frequently in COVID-19-associated pneumonia – 57.0% compared with 9.0% (OR=6.33, CI [2.98-13.48]) ($p<0.05$).

Typical CT signs of coronavirus pneumonia included multiple lobular ground-glass opacities and subsegmental lung consolidations, which suggest homogeneous increased attenuation of the lung parenchyma with obscuration of underlying vessels; ground-glass opacity – elevated attenuation without vascular obscuration – indicates edema and thickening of the interlobular septum; ground-glass opacity plus reticular pattern – a reticular shadow on the background of ground-glass opacity and thickened lungs – indicates interlobular septal thickening resulting from ground-glass opacity, which eventually turns into a subpleural line; the sign of microvascular dilatation (dilated small vessels within lesions), characterized by enhanced blood flow to inflamed areas; fibrous stripes (irregular linear opacities), indicating local inflammatory absorption and residual fibrosis; a subpleural line (a 2-5 cm arc-shaped linear opacity parallel to the chest wall) or a subpleural transparent line (a thin clear line between the lesion and the visceral pleura).

Lung involvement was classified as predominantly peripheral (one-third of the lung), central (two-thirds of the lung), or mixed – peripheral and central. Bronchial changes were of two types: air bronchogram (air-filled bronchus visible within lung

infiltrates) and bronchial deformation, which indicates local inflammation and traction of the bronchus inward. Pleural changes were classified into: signs of pleural retraction (lesions located near the visceral pleura causing its traction inward) or pleural effusion. The frequency of pleural changes was higher in group 1, whereas bronchial changes were more frequent in group 2.

Thus, in COVID-19-associated pneumonia, bilateral polysegmental lung lesions occurred more frequently than unilateral ones, accompanied by reactive pleural inflammation. In most patients of group 1, involvement of the lower and middle lung segments was detected. The most common pulmonary changes were fibrotic alterations, ground-glass opacities with reticular pattern, and consolidation. Among bronchial abnormalities, air bronchogram was common, whereas bronchial deformation was observed less frequently. Pleural changes predominantly included signs of pleural retraction and pleural thickening. The obtained data correspond to the findings of numerous authors regarding radiological and tomographic characteristics of lung tissue injury in COVID-19.

Analysis of the spirometry results in patients with moderate-severity viral-bacterial pneumonia compared with those with COVID-19-associated pneumonia demonstrated more pronounced and statistically significant reductions in respiratory flow parameters. In patients of Group 2, the pre-bronchodilator FEV_1 was significantly lower by 18.1% compared with the control values ($p<0.05$). However, the mean post-bronchodilator FEV_1 remained 19.3% lower than in the control group ($p<0.05$). The increase in FEV_1 after salbutamol administration in Group 2 was 5.6%, indicating an irreversible bronchial obstructive syndrome. In Group 1, the flow parameters significantly differed from the control values only after salbutamol inhalation – the FEV_1 was 7.9% lower ($p<0.05$). The FVC significantly changed only in Group 2 it was 12.0% lower than in the control group ($p<0.05$). Changes in Group 1 were not statistically significant. At the same time, in Group 1 a significant reduction in VC by a factor of 1.2 ($p<0.05$) was found, which indicates restrictive pulmonary changes due to pneumonia. Thus, we concluded that the course of VBP is accompanied by bronchial obstructive syndrome caused by the impact of viral–bacterial infection on the bronchoalveolar system and by sensitization of the organism to pathogens and their metabolic products. The reduced reversibility of obstruction may also be attributed to comorbid COPD in this group of patients ($p<0.05$). Meanwhile, patients with CAP-S demonstrated significant restrictive changes associated with predominantly bilateral infiltrative lung involvement as a result of pneumonia.

Analysis of sputum cultures in patients with CAP-VB that developed on the background of influenza, parainfluenza, and RSV during the 2023-2024 epidemic season revealed the following diversity of isolated bacterial pathogens that accompanied the course of viral pneumonia as co-infection or superinfection. The most common pathogens of this pneumonia were K. pneumoniae (31.0%), S. pneumoniae (37.0%), S. pyogenes (22.0%), S. aureus (21.0%), H. influenzae (35.0%), M. catarrhalis (17.0%), all of which significantly exceeded the detection frequency observed in CAP-S ($p<0.05$). Thus, pneumonia occurring on the background of influenza, parainfluenza,

and RSV, owing to the proven high rate of co-infection and superinfection, has a mixed viral-bacterial nature and differs in its course from pneumonia associated with COVID-19.

The calculated index of bacterial and fungal co- and superinfections in moderate CAP-S was low, within 17.0%, whereas in VBP the co-/superinfection index reached 52.0%. The pathogens most commonly associated with COVID-19 were Streptococcus pneumoniae (11.0%), K. pneumoniae (10.0%), S. aureus (8.0%), Mycoplasma pneumoniae (9.0%), H. influenzae (7.0%), while other bacteria were isolated in 1.0-4.0% of cases. The fungi most frequently causing co-infection in CAP-S were Aspergillus spp. (8.0%) and Candida spp. (2.0%). The findings obtained in this study are consistent with data reported by other researchers.

Analysis of comorbid conditions showed that patients with pneumonia had a number of modifying factors and risk factors for severe pneumonia related to existing comorbid pathology. Thus, twice as many patients in Group 1 (42.0%) were overweight compared with Group 2 (21.0%) (OR=2.0, CI [1.11-3.62]) ($p<0.05$). Meanwhile, 4.3 times more patients (13.0%) in the same group had obesity (compared with 3.0% in Group 2) (OR=4.33, CI [1.19-15.67]) ($p<0.05$). Individuals who are overweight or obese have reduced anti-infective immunity; thus, this comorbidity is a risk factor for severe pneumonia. There was also a higher rate of baseline type 2 diabetes mellitus in Group 1 compared with Group 2 (a 2.7-fold difference) (OR=2.71, CI [1.09-6.74]) ($p<0.05$). A substantial proportion of Group 1 patients (49.0%) had hyperlipidemia and dyslipidemia, modifiable risk factors for atherosclerosis, which in Group 2 were observed 2.9 times less frequently (12.0%) (OR=2.88, CI [1.56-5.34]) ($p<0.05$).

In patients of Group 1, a number of cardiovascular diseases were identified that could contribute to the complicated course of COVID-19. Thus, 49.0% of patients had pre-existing arterial hypertension, which was 4.1 times higher than the proportion of patients with hypertension in Group 2 (12.0%) (OR=4.08, CI [2.05-8.14]) ($p<0.05$). A total of 31.0% of patients in Group 1 had various forms of coronary artery disease compared with 8.0% in Group 2, which represents a 3.9-fold difference (OR=3.88, CI [1.69-8.84]) ($p<0.05$). The prevalence of arrhythmias was almost identical in both groups (7.0% and 5.0% in Groups 1 and 2, respectively), including extrasystolic arrhythmia and permanent atrial fibrillation. In patients of Group 1, acute myocarditis developed 6.8 times more frequently in the setting of COVID-19 compared with Group 2 (OR=6.80, CI [2.55-18.10]) ($p<0.05$). Signs of left-ventricular heart failure were recorded 2.7 times more often in Group 1 compared with Group 2 (OR=2.67, CI [1.18-6.02]) ($p<0.05$). The prevalence of other rheumatologic pathology was nearly the same in both groups (12.0% and 7.0% in Groups 1 and 2, respectively), including rheumatic heart disease, osteoarthritis of large joints, and the articular form of psoriasis.

In addition, in Group 1 the frequency of chronic kidney disease (CKD) stage I-II was 4.7 times higher (28.0% vs. 6.0%), which progressed under the influence of COVID-19 (OR=4.67, CI [1.85-11.76]) ($p<0.05$), thereby worsening the course of pneumonia. A higher incidence of acute reactive hepatitis was also registered in Group 1 (41.0% vs. 6.0%) (OR=6.80, CI [2.78-16.81]) ($p<0.05$), as well as a higher frequency

(32.0% vs. 5.0%, i.e., a 6.4-fold increase) of chronic pancreatitis in the acute phase (OR=6.40, CI [2.39-17.09]) ($p<0.05$), and metabolically associated steatotic liver disease (OR=2.33, CI [1.37-3.96]) ($p<0.05$). During the course of COVID-19, clinical manifestations of irritable bowel syndrome were documented in 52.0% of patients in Group 1 compared with 11.0% in Group 2 (OR=4.73, CI [2.33-9.57]) ($p<0.05$). It should be emphasized that IBS symptoms with diarrhea persisted in half of the Group 1 patients at the time of discharge. These findings partially coincide with published data on comorbid conditions in COVID-19 patients, while some of the findings obtained in our study are novel.

Meanwhile, in Group 2 a higher prevalence of underlying pulmonary pathology was found compared with Group 1. The frequency of bronchial asthma in Group 2 was twice that in Group 1 (OR=2.0, CI [0.86-4.66]) ($p>0.05$). The prevalence of COPD in Group 2 was significantly higher, being 3 times that of Group 1 (OR=3.0, CI [1.29-6.99]) ($p<0.05$), indicating the ability of CAP-VB pathogens to induce sensitization and contribute to inflammatory edema of the bronchial wall with the development of obstruction de novo, or to trigger exacerbations of COPD and asthma. This was also facilitated by the higher prevalence of tobacco smoking, 13.0% in Group 1 versus 31.0% in Group 2, a 2.4-fold difference (OR=2.38, CI [1.18-4.82]) ($p<0.05$), which contributed to the development of bronchopulmonary complications in Group 2.

Thus, the underlying general somatic pathology that contributed to the complicated course of COVID-19 in Group 1 included a higher frequency of excess body weight and comorbid obesity, hyperlipidemia and dyslipidemia, higher prevalence of type 2 diabetes mellitus, arterial hypertension, coronary artery disease, acute myocarditis, heart failure, CKD, metabolically associated steatotic liver disease, acute reactive hepatitis, pancreatitis, and IBS. In contrast, patients in Group 2 exhibited a higher prevalence of smoking, bronchial asthma, and COPD.

In patients with a laboratory-confirmed diagnosis of COVID-19, anemic syndrome was detected in 32.07% of cases, indicating a high incidence of its development among infected individuals. This figure exceeds the average population prevalence of anemia and demonstrates the significant impact of viral inflammation on the hematopoietic system. Anemia in patients with COVID-19 may develop due to a combination of several mechanisms, the direct cytopathic effect of the virus, tissue hypoxia, activation of the cytokine cascade, and disturbances in iron metabolism. This condition often remains underestimated in clinical practice because its symptoms (weakness, dyspnea, tachycardia) may be masked by manifestations of the underlying disease. At the same time, anemia exacerbates systemic hypoxia, contributes to organ dysfunction, and increases the risk of complications. Thus, the high detection rate of anemic syndrome in COVID-19 confirms the appropriateness of including hematological assessment in the standard evaluation of such patients.

Among patients with COVID-19, mild (45.5%) and moderate (32.6%) anemia predominated, whereas the severe form was recorded in 21.9% of cases. This distribution reflects the progressive, multifactorial nature of anemic syndrome during the infectious process. Mild forms may result from transient functional iron deficiency,

whereas severe forms arise from pronounced systemic inflammation, suppression of erythropoiesis, or the presence of comorbid conditions. The frequency of severe anemia is especially high among individuals with concomitant liver, kidney, or cardiovascular diseases. Importantly, the severity of anemia correlates with the duration of hospitalization and the risk of complications. Therefore, stratification of patients according to the severity of anemic syndrome is essential for predicting the clinical course of COVID-19.

In middle-aged patients, mild anemia (47.9%) was the most frequently documented, whereas among older individuals, moderate (36.7%) and severe (20.1%) forms prevailed. This indicates an age-related dependence of erythropoiesis disorders caused by reduced regenerative potential of the bone marrow. In addition, older age is more often associated with nutrient deficiencies, reduced sensitivity to erythropoietin, and accumulation of chronic diseases. Age-related comorbidity creates a background for a more severe course of COVID-19 with the development of systemic hypoxia and hematological disorders. The obtained data confirm that age is an independent risk factor for both anemia and severe disease progression. Thus, monitoring the hematological status is particularly important in elderly patients.

Female patients with COVID-19 more often presented with moderate anemia (35.1%), whereas in males, the severe form predominated (24.3%). These gender differences can be explained by both physiological and pathophysiological factors. In women, fluctuations in estrogen levels and specific features of iron metabolism contribute to a greater predisposition to moderate forms of anemia. In men, the more severe course may be associated with a higher prevalence of concomitant cardiovascular diseases and increased inflammatory reactivity. It has also been shown that men more frequently experience severe COVID-19, which may further intensify hypoxic disturbances. These observations highlight the need for a gender-oriented approach to assessing the severity and treatment of anemia in COVID-19 patients.

Among patients hospitalized with COVID-19 who were diagnosed with anemic syndrome, the incidence of viral-bacterial pneumonia was 72%, whereas among individuals with normal hemoglobin levels it was only 38%. Such a substantial difference in complication rates indicates the presence of a close pathophysiological relationship between anemia and susceptibility to secondary infection of the lower respiratory tract. In patients with anemia, the reduced oxygen-transporting capacity of the blood leads to tissue hypoxia, which significantly affects the functional state of the immune system, particularly the activity of neutrophils, macrophages, and lymphocytes. Hypoxia inhibits the neutrophil oxidative burst – a key mechanism of intracellular bacterial killing, thereby reducing the effectiveness of phagocytosis and allowing pathogens to colonize the respiratory tract more easily. At the same time, anemia triggers systemic inflammation with excessive release of cytokines (IL-6, TNF-α), which leads to injury of the bronchial and alveolar epithelium, formation of microvascular thrombosis, and further deepening of hypoxia. As a result, favorable conditions arise for the attachment of bacterial flora, leading to the development of mixed viral-bacterial

pneumonias, which have a more severe course and more frequently require the use of broad-spectrum antibiotics.

Additionally, anemia contributes to the dysregulation of erythropoietin, which has not only hematopoietic but also cytoprotective and immunomodulatory functions, thereby reducing the resilience of lung tissue to oxidative stress. This enhances endothelial dysfunction, one of the key mechanisms underlying COVID-19 complications, including microcirculatory thrombosis in the lungs. Patients with a combination of anemia and viral-bacterial pneumonia more often exhibit a prolonged inflammatory course, a greater need for oxygen therapy or mechanical ventilation, and a higher risk of fatal outcomes. Therefore, anemia should be regarded not merely as an accompanying condition but as one of the independent predictors of COVID-19 severity, necessitating mandatory diagnosis and correction. Incorporating monitoring of hemoglobin, ferritin, and inflammatory markers into the standard management algorithm for COVID-19 patients allows for the identification of individuals at increased risk of secondary complications and prevention of the development of concomitant bacterial pneumonia in a timely manner.

The clinical analysis of COVID-19 progression in hospitalized patients demonstrated that anemic syndrome is one of the common and significant systemic manifestations of the disease, which is often underestimated during diagnostic assessment. Its clinical symptomatology predominantly corresponds to the circulatory-hypoxic type, reflecting reduced blood capacity to deliver oxygen to tissues. The main manifestations include general weakness, rapid fatigability, dyspnea with minimal exertion, tachycardia, dizziness, pallor of the skin and mucous membranes. In some cases, patients experience headaches, orthostatic reactions, palpitations that intensify in an upright position, as well as increased drowsiness due to cerebral hypoxia.

Such symptoms are often interpreted by physicians as manifestations of respiratory failure or intoxication syndrome characteristic of COVID-19, which complicates timely detection of anemia. As a consequence, patients receive only symptomatic or antiviral therapy without adequate correction of hematopoietic disorders. The absence of treatment for anemia leads to the deepening of tissue hypoxia, increased load on the cardiovascular system, and activation of compensatory mechanisms (including tachycardia and increased cardiac output), which depletes the organism's reserves. In addition, hypoxia serves as a powerful stimulator of systemic inflammation, enhancing the synthesis of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and promoting oxidative stress. This causes further endothelial injury, increased vascular permeability, and microthrombosis – key mechanisms in the pathogenesis of severe forms of COVID-19. The vicious cycle "anemia → hypoxia → inflammation → endothelial dysfunction" aggravates the severity of the patient's condition, increasing the risk of organ damage (myocardium, kidneys, brain).

Timely recognition of anemic symptoms and the inclusion of laboratory indicators (hemoglobin, hematocrit, ferritin, reticulocytes) in the initial screening of patients with COVID-19 likely allows the identification of latent anemia, which often precedes the development of complications. The integration of clinical, hematological,

and pathogenetic data is critically important for a comprehensive assessment of the patient's condition and for choosing a therapeutic strategy. Anemia in the context of COVID-19 should be regarded not as a secondary phenomenon, but as an integral component of the systemic response of the organism, one that significantly affects the course, prognosis, and duration of recovery from the disease.

In most hospitalized patients with COVID-19, anemia of inflammatory origin is detected, which pathogenetically corresponds to anemia of chronic disease (ACD). This type of anemia develops not due to iron deficiency per se, but because of impaired iron utilization under conditions of prolonged systemic inflammation. An elevated ferritin level in such patients reflects not only the presence of iron stores but also activation of the macrophage system, which, under the influence of cytokines (primarily interleukin-6, TNF-α, IL-1β), stimulates uptake and sequestration of iron in the reticuloendothelial cells of the liver, spleen, and bone marrow. As a result, iron becomes functionally unavailable for erythropoiesis despite normal or increased stored levels. At the same time, systemic inflammation activates the synthesis of hepcidin, the main regulator of iron metabolism, which blocks iron release from macrophages and enterocytes. This leads to a decrease in circulating plasma iron, even when iron stores are sufficient, further worsening anemia.

As a result, erythropoietic activity of the bone marrow decreases because iron is not available for hemoglobin synthesis. An additional contributing factor is the suppression of erythropoietin production in the kidneys by pro-inflammatory cytokines, primarily IL-6, as well as decreased sensitivity of erythroid cells to its stimulatory effect. All this forms the typical biochemical profile of ACD in COVID-19: low hemoglobin, reduced serum iron, low transferrin saturation, but elevated ferritin and normal or reduced total iron-binding capacity.

Such anemia has an adaptive character, as iron sequestration is part of the immune defense that limits iron availability to pathogenic microorganisms that require it for growth. However, in COVID-19, when inflammation becomes systemic (cytokine storm), this mechanism becomes pathogenetically harmful and deepens hypoxia, contributing to the progression of lung, cardiac, and renal injury.

Moreover, in COVID-19, ferritin functions not only as a marker of iron stores but also as an acute-phase protein that directly reflects the activity of systemic inflammation. Its elevation correlates with disease severity, levels of C-reactive protein, D-dimer, and IL-6 concentration. High ferritin levels are associated with the development of the "hyperferritinemic syndrome," which is a predictor of cytokine storm and multiorgan failure. Thus, evaluation of ferritin in combination with hemoglobin levels has not only diagnostic but also prognostic significance.

Thus, anemia in COVID-19 is a systemic phenomenon in which inflammation, disturbances of iron metabolism, oxidative stress, and erythropoietin deficiency coexist within a unified pathogenic mechanism. It is a marker of disease severity, and its presence requires an individualized therapeutic strategy. Correction of anemia of chronic disease should not be limited merely to the administration of iron preparations, but must include control of inflammation, optimization of energy metabolism,

correction of hypoxia, and, when necessary, the use of erythropoiesis-stimulating agents. Such a comprehensive approach can improve hematological parameters, reduce the severity of COVID-19, accelerate recovery, and decrease the risk of complications.

In hospitalized patients with COVID-19, a significant increase in procalcitonin levels was established, which showed a reliable positive correlation with the severity of anemia. This relationship indicates that both processes – systemic inflammation and impaired erythropoiesis – are closely interconnected in the progression of severe forms of COVID-19. Procalcitonin is an acute-phase protein whose synthesis is activated under the influence of pro-inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor α. Under normal conditions, its concentration in the blood is low, but in systemic inflammation or sepsis, characteristic of severe COVID-19, procalcitonin levels increase dozens of times. Its high level in COVID-19 patients with concomitant anemia indicates not only possible bacterial coinfection but also hyperactivation of the cytokine cascade that underlies the cytokine storm. The latter causes endothelial damage, increased vascular permeability, mitochondrial dysfunction, and intensification of oxidative stress. Anemia in such conditions exacerbates tissue hypoxia, which further stimulates the release of pro-inflammatory mediators. Thus, a vicious cycle of "inflammation – hypoxia – progression of inflammation" is formed, in which anemia acts as a factor that mutually aggravates the course of infection.

Oxidative stress caused by oxygen deficiency leads to peroxidative damage of erythrocyte membranes, reducing their lifespan and impairing deformability, which further decreases the efficiency of oxygen delivery. Under the influence of systemic inflammation, erythropoietin activity and bone marrow erythropoiesis are suppressed, slowing the restoration of normal hemoglobin levels. As a result, patients with high procalcitonin levels experience a more prolonged course of anemia, respond more slowly to treatment, and have a higher risk of developing respiratory failure and organ injury. In addition, the increase in procalcitonin in such patients may result from systemic endotoxemia, which develops due to intestinal dysbiosis or microbial translocation caused by hypoxic-inflammatory injury of mucosal barriers. This enhances IL-6 secretion and stimulates hepcidin synthesis, which in turn blocks iron release into the bloodstream and deepens anemia of chronic inflammation. Thus, a high procalcitonin level can simultaneously serve as an indicator of inflammation, endotoxemia, and metabolic disturbances within the "iron – erythropoiesis" system.

Regular determination of procalcitonin in patients with COVID-19 may have substantial clinical and prognostic significance. Its dynamic elevation may indicate worsening of the patient's condition, the onset of secondary bacterial infection, or the development of a cytokine storm. Conversely, gradual decline in procalcitonin during the course of illness reflects the effectiveness of anti-inflammatory or antibacterial therapy. Therefore, monitoring procalcitonin should be an integral component of laboratory evaluation in patients with COVID-19, especially when anemia is present.

Thus, the assessment of procalcitonin not only clarifies the degree of systemic inflammation but also helps to evaluate the risk of hypoxic complications, optimize antibacterial therapy, and timely adjust anemia treatment. This biomarker is a valuable

integrative indicator of the pathogenetic interplay between inflammation, anemia, and hypoxia that determines disease severity and prognosis in patients with COVID-19.

The presence of anemia in patients with COVID-19 was accompanied by a significant prolongation of the duration of inpatient treatment, an average of 14.8±2.3 days versus 10.2±1.9 days in patients without anemia ($p<0,05$). This result is explained by a more severe course of the disease, slower restoration of oxygenation, and a higher risk of developing complications. Anemic hypoxia leads to cellular energy deficiency, reduced tolerance to antiviral therapy, and delayed reparative processes. In addition, patients with anemia more frequently experience thromboembolic episodes and bacterial infections, which also prolong hospitalization. This tendency has both clinical and economic significance, as extended treatment increases the burden on the healthcare system. Therefore, monitoring hematological parameters and correction of anemia are important components of the management strategy for patients with COVID-19.

The obtained results emphasize the key role of comprehensive laboratory assessment of inflammatory biomarkers – ferritin, procalcitonin, and C-reactive protein – in patients with COVID-19, especially in the presence of anemic syndrome. According to numerous clinical studies, these biomarkers are the most informative for evaluating the systemic inflammatory response, the degree of tissue injury, and the severity of the disease. Integration of these indicators into a unified diagnostic algorithm allows not only the differentiation of anemia of chronic disease from deficiency anemia but also justified avoidance of irrational prescription of iron-containing preparations, which may be ineffective or even harmful in systemic inflammation due to enhancement of oxidative stress. Comprehensive monitoring of the dynamics of ferritin, procalcitonin, and C-reactive protein allows assessment of not only inflammatory activity but also prediction of complications such as cytokine storm, thrombotic events, or the development of bacterial pneumonia. At the same time, these indicators serve as markers of therapeutic effectiveness: their decline reflects stabilization of the immune response and reduction of systemic hypoxia.

Thus, the laboratory assessment of inflammatory biomarkers in patients with COVID-19 and anemic syndrome has dual significance, both diagnostic and prognostic. It allows timely detection of anemia of chronic inflammation, optimization of therapeutic strategies, avoidance of unjustified prescription of iron preparations, and ultimately increases the effectiveness of treatment in patients with severe forms of COVID-19.

Prospects for further research in this area involve in-depth study of the relationships between systemic inflammation, iron metabolism, and the development of anemic syndrome in patients with COVID-19. In the future, it is advisable to conduct prospective multicenter cohort studies with long-term monitoring of the dynamics of ferritin, procalcitonin, C-reactive protein, hepcidin, transferrin saturation, indicators of erythropoiesis, and functional activity of the bone marrow. Such studies will make it possible to establish the sequence of pathogenetic events, from activation of the cytokine cascade to the formation of anemia of chronic inflammation, and to clarify its clinical significance.

A separate direction of research should concern the mechanisms regulating the "hepcidin – ferroportin" axis in SARS-CoV-2-induced inflammation. A combination of molecular and clinical methods, including transcriptomics, proteomics, metabolomics, and cytokine panels, will make it possible to identify phenotypes of inflammatory anemia and potential targets for therapeutic correction. Another promising area is the study of the role of the gut microbiome, microbial translocation, and endotoxemia in maintaining systemic inflammation and dysregulation of iron metabolism.

Randomized clinical trials are required to assess the effectiveness of various therapeutic strategies (anti-inflammatory therapy, hepcidin-modifying agents, erythropoiesis stimulators, iron preparations, or anticytokine agents) taking into account baseline ferritin levels and the inflammatory profile. In this context, it is important to develop prognostic models and clinical decision-making algorithms based on the integration of inflammatory biomarkers and anemia indicators using machine learning methods. Equally important is the standardization of analytical approaches, reference intervals, and threshold values of biomarkers (ferritin, procalcitonin, hepcidin), which will ensure the comparability of results between different centers. It is also necessary to expand research to subgroups of patients with comorbidities, including diabetes mellitus, chronic kidney disease, and obesity, in order to assess their impact on erythropoiesis and the course of anemia.

Further studies should also encompass an analysis of the long-term consequences of COVID-19 (the persistence of anemia and its impact on the patient's functional status, cardiovascular events, and quality of life). Ultimately, the integration of clinical, laboratory, and molecular approaches will allow the transition from a descriptive to a cause-and-effect model of anemic syndrome in COVID-19, which will contribute to the development of personalized treatment strategies and prevention of its complications.

Another promising direction for future research is a comprehensive evaluation of therapeutic strategies for managing patients with community-acquired pneumonia associated with coronavirus disease, taking into account the impact of comorbidities involving the cardiovascular, bronchopulmonary, gastrointestinal, and hepatobiliary systems. It is advisable to design multicenter randomized trials comparing standard therapy (empirical antibacterial regimens, corticosteroids when indicated, oxygen therapy) with personalized algorithms stratified according to risk profile and comorbidity burden. For cardiovascular comorbidities, additional studies are needed to determine optimal antiplatelet regimens, appropriate fluid management, and safe corticosteroid dosing considering the risk of decompensation of underlying conditions. Promising areas include economic assessments of the cost-effectiveness of personalized care pathways (including telemedicine and outpatient monitoring), implementation research aimed at reducing variability of care between institutions, as well as evaluation of long-term outcomes (90-180 days) such as the frequency of lung fibrosis, decreased exercise tolerance, and quality of life. The combination of randomized trials, registry data, and machine learning approaches will help develop evidence-based, comorbidity-oriented treatment algorithms for community-acquired pneumonia in patients with

COVID-19, enhancing safety, reducing resource utilization, and improving clinical outcomes for diverse patient groups.

CONCLUSIONS

1. The gender distribution of individuals treated for moderate community-acquired pneumonia associated with COVID-19 demonstrated a significant predominance of women (62.0%) over men (38.0%) ($p<0.05$). Among patients with community-acquired viral-bacterial pneumonia, the female-to-male ratio was 53.0% vs. 47.0% ($p>0.05$). According to age distribution, persons aged 51 to 75 years more frequently developed moderate COVID-19-associated pneumonia (49.0%) ($p<0.05$), whereas viral-bacterial community-acquired pneumonia occurred more often in younger individuals under 50 years of age (51.0%) ($p<0.05$). The age group over 75 years showed similar rates of CAP-S and CAP-VB ($p>0.05$).
2. The clinical features of COVID-19 pneumonia, compared with viral-bacterial pneumonia, included a higher frequency of complaints such as intense chest pain during breathing and coughing (2.0-fold), fever (1.7-fold), anosmia (5.6-fold), severe sore throat with odynophagia (26-fold), inspiratory dyspnea with increasing intensity (1.7-fold), myalgia (4.9-fold), asthenia (3.6-fold), intense headache at disease onset (2.2-fold), short episodes of loss of consciousness (9.3-fold), nausea (2.2-fold), and diarrhea (8.6-fold) ($p<0.05$). Patients with CAP-S also demonstrated a significantly higher frequency of body temperature above 38.5°C (2.4-fold), heart rate above 90 bpm (2.6-fold), respiratory rate above 25 per minute (2.9-fold) ($p<0.05$), and oxygen saturation levels of 90-92% (1.7-fold) ($p<0.05$).
3. In 65.0% of patients with CAP-S leukopenia was detected (vs. 32.0% in CAP-VB), lymphocytopenia was found in 87.0% (vs. 27.0%), thrombocytopenia in 69.0% (vs. 31.0% in CAP-VB), as well as a higher frequency of elevated ESR (1.9-fold) ($p<0.05$). CAP-S was characterized by greater inflammatory intensity, as indicated by higher frequencies of hyperfibrinogenemia (2.7-fold) ($p<0.05$), hyperferritinemia (3.7-fold), and elevated C-reactive protein levels above 20 mg/L (2.6-fold) ($p<0.05$), substantially exceeding systemic inflammation observed in CAP-VB.
4. Coronavirus disease complicated by moderate pneumonia was accompanied by liver parenchymal injury with the development of acute reactive hepatitis manifested by cytolytic, cholestatic, and mesenchymal-inflammatory syndromes of mild to moderate activity, as well as increased blood creatinine and urea levels ($p<0.05$), with some cases progressing to acute kidney injury and others showing worsening of pre-existing chronic kidney disease during COVID-19.
5. In patients with CAP-S, radiological examination more often revealed bilateral pneumonia (66.0% vs. 34.5% in CAP-VB), which was 1.9-fold more common in CAP-S, with predominant involvement of the lower and middle lung segments, formation of “ground-glass opacity” with enhanced reticular pattern, consolidation, and diffuse fibrotic changes ($p<0.05$), as well as pleural inflammatory reaction (6.3-fold) – 57.0% vs. 9.0% ($p<0.05$). The course of CAP-VB was more frequently accompanied by bronchial obstructive syndrome ($p<0.05$), while patients with CAP-S demonstrated significant restrictive changes

in pulmonary function tests due to bilateral infiltrative lung involvement and pneumosclerosis.

6. The index of co-infections and superinfections with bacterial and fungal pathogens in moderate CAP-S was within 17.0%, whereas in CAP-VB it reached 52.0%. The most common pathogens of CAP-VB etiology were *K. pneumoniae* (31.0%), *S. pneumoniae* (37.0%), *S. pyogenes* (22.0%), *S. aureus* (21.0%), *H. influenzae* (35.0%), and *M. catarrhalis* (17.0%), which significantly exceeded their detection rate in CAP-S ($p<0,05$). The pathogenic microorganisms most frequently associated with COVID-19 were *Streptococcus pneumoniae* (11.0%), *K. pneumoniae* (10.0%), *S. aureus* (8.0%), *Mycoplasma pneumoniae* (9.0%), *H. influenzae* (7.0%), while other bacteria were isolated in 1.0-4.0% of cases. The most common fungi causing co-infections in CAP-S were *Aspergillus* spp. (8.0%) and *Candida* spp. (2.0%).
7. In patients with community-acquired pneumonia associated with COVID-19, compared with CAP-VB, there was a predominance of risk factors for severe pneumonia, including a higher frequency of excess body weight and comorbid obesity, hyperlipidemia and dyslipidemia, and a higher prevalence of comorbid systemic diseases: type 2 diabetes mellitus, arterial hypertension, coronary artery disease, acute myocarditis, heart failure, chronic kidney disease, metabolic-associated steatotic liver disease, acute reactive hepatitis, pancreatitis, and irritable bowel syndrome with diarrheal syndrome ($p<0.05$). In contrast, patients with CAP-VB had a higher frequency of smoking and a higher prevalence of comorbid asthma and COPD ($p<0.05$).
8. Anemic syndrome complicated the course of coronavirus disease in approximately one-third of hospitalized patients with SARS-CoV-2 infection, indicating its high prevalence among individuals with severe COVID-19. In the analyzed medical records, mild (45.5%) and moderate (32.6%) degrees of concomitant anemia were most frequently observed, which can likely be explained by timely diagnosis and effective correction of reduced hemoglobin levels in this patient category, preventing progression to severe anemia.
9. The frequency of moderate and severe anemia in COVID-19 was significantly higher among elderly patients (60-68 years), which is likely associated with age-related changes in normal hematopoiesis, alterations in iron metabolism, reduced sensitivity to erythropoietin, and a higher prevalence of chronic comorbid conditions in older age groups.
10. The presence of anemia in patients with COVID-19 was associated with a marked increase in the frequency of viral-bacterial pneumonia, 72% compared with 38% in patients without anemia, allowing anemia to be considered a potential additional risk factor for pulmonary complications. This may be attributed to impaired oxygenation of the pulmonary parenchyma under conditions of anemic hypoxia, the development of hypoxic alveolar injury, and progression of respiratory failure.

11. Among the analyzed medical records, anemia was predominantly normocytic and normochromic in most cases (over 83%), indicating its primarily inflammatory nature in patients with COVID-19. This is confirmed by elevated ferritin levels combined with reduced serum iron and decreased total iron-binding capacity, which together represent signs of functional iron deficiency characteristic of anemia of chronic disease.
12. Anemia in patients with COVID-19 was associated with a statistically significant increase in the duration of hospitalization (14.8±2.3 days versus 10.2±1.9 days, $p<0.05$), which correlated with the increasing severity of anemia. This relationship is explained by the deepening of hypoxia against the background of anemic syndrome, a higher frequency of concomitant comorbidities, impaired immune response, and an increased risk of complications. In addition, the observed rise in procalcitonin levels with decreasing hemoglobin indicates an interrelationship between anemia and the intensity of the inflammatory process, which determines the clinical severity of patients' condition.

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