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Биомаркеры и прогностические модели тяжёлого течения COVID-19 в сравнении с сепсисом другой этиологии

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АННОТАЦИЯ

В наиболее тяжёлой форме COVID-19 имеет общие патофизиологические, иммунологические, метаболические и клинические характеристики с классическим бактериальным сепсисом. У пациентов с тяжёлым течением COVID-19 наблюдаются проявления заболевания, характерные для сепсиса, включая острый респираторный дистресс-синдром и полиорганную недостаточность. Однако результаты исследований указывают на то, что инфекция COVID-19, вызывающая острый респираторный дистресс-синдром и септический синдром, более фатальна, чем септический синдром другой этиологии. Коронавирус SARS-CoV-2 первоначально поражает лёгкие, но при COVID-ассоциированном сепсисе причиной большинства летальных исходов является последующее поражение нескольких органов. Становится всё более очевидным, что многие пациенты, умершие от COVID-19, умерли из-за сепсиса — опасной для жизни дисфункциональной реакции на инфекцию, которая сопровождается дыхательной и полиорганной недостаточностью.

У пациентов с тяжёлыми инфекциями SARS-CoV-2 и сепсисом от всех причин обнаруживаются перекрывающиеся молекулярные характеристики. Эндотипы, отражающие различные этиологии сепсиса, идентифицированы в группах пациентов с тяжёлым течением COVID-19. Протеомика и транскриптомика цельной крови оказались полезными для идентификации патогенетических механизмов и мультимолекулярных сигнатур COVID-ассоциированного сепсиса и сепсиса другой этиологии, что позволяет разработать более конкретные критерии для ранней диагностики, классификации пациентов и обоснования терапевтического выбора.

Обнаружение эндотипов сепсиса у пациентов с COVID-19 подразумевает, что они могут быть полезны для стратификации клинического риска у пациентов с COVID-ассоциированным сепсисом и что существует потенциальная возможность лечить этих пациентов с помощью таргетной иммуномодулирующей терапии, которая корректирует дисфункциональные иммунные процессы, характерные для определённого эндотипа.

Ключевые слова: COVID-19; сепсис; иммунная дисфункция; острый респираторный дистресс-синдром; полиорганная недостаточность; коронавирус SARS-CoV-2; эндотип; протеомика; транскриптомика; биомаркер, молекулярная сигнатура.

Как цитировать

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Biomarkers and prognostic models for severe COVID-19 in comparison with other etiologies of sepsis

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ABSTRACT

Severe COVID-19 shares pathophysiological, immunological, metabolic, and clinical features with classic bacterial sepsis. Patients with severe COVID-19 have sepsis-like manifestations, such as acute respiratory distress syndrome and multiple organ failure. However, research indicates that COVID-19 leads to acute respiratory distress syndrome and that septic syndrome is more fatal than septic syndrome of other etiologies. SARS-CoV-2 initially infects the lungs; however, in COVID-19-associated sepsis, the majority of deaths are caused by the subsequent involvement of multiple organs. Many patients who died because of COVID-19 died from sepsis, a life-threatening dysfunctional response to infection that is accompanied by respiratory and multiple organ failure.

Overlapping molecular characteristics are found in patients with severe COVID-19 and sepsis from all causes. Endotypes that reflect different etiologies of sepsis have been identified in patients with severe COVID-19. Whole-blood proteomics and transcriptomics are useful in identifying the pathogenetic mechanisms and multimolecular signatures of COVID-associated sepsis and other sepsis, which allow for the development of more specific criteria for early diagnosis, patient classification, and therapeutic choices.

The detection of sepsis endotypes in patients with COVID-19 implies that sepsis endotypes may be useful for clinical risk stratification in COVID-associated sepsis and the potential opportunity to treat these patients with targeted immunomodulatory therapies that can correct endotype-specific dysfunctional immune processes.

Keywords: COVID-19; sepsis; immune dysfunction; acute respiratory distress syndrome; multiple organ failure; coronavirus SARS-CoV-2; endotype; proteomics; transcriptomics; biomarker; molecular signature.

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BACKGROUND

In 20% of patients with coronavirus disease 2019 (COVID-19; hereinafter referred to as COVID), the disease progresses to a severe (requiring supplemental oxygen or intensive care) and extremely severe form [acute respiratory distress syndrome (ARDS), sepsis, septic shock, and multiple organ dysfunction] or death; however, existing prognostic models cannot identify such patients because laboratory markers are late indicators of severity, and by the time the levels of these markers become abnormal, the disease has already progressed [1]. In-hospital mortality rates from sepsis and septic shock are 35% and 52%, respectively [2]. The mortality rate from sepsis increased during the COVID pandemic [3], and >20% of sepsis survivors died over the next 2 years, which is not explained by their presepsis health status; therefore, the World Health Organization declared sepsis to be a global health priority [4].

The clinical manifestations and laboratory parameters of sepsis and COVID are very similar [5]; thus, recommendations for the treatment of patients with severe COVID have been developed directly from similar guidelines for sepsis [6]. However, differences also exist. In patients with COVID, sepsis is associated primarily with a pulmonary focus, whereas in patients without COVID, the most frequently diagnosed sites were abdominal (35%), pulmonary (20%), and urogenital (12%) regions. Septicemia was common in both groups (48% in patients with COVID, 53% in patients without COVID), with staphylococcus as the most commonly isolated pathogen. Sepsis shock upon admission to the intensive care unit (ICU) was registered in 29% of the patients and occurred more often in patients with non-COVID sepsis (43% vs. 14%, $p < 0.05$). In addition, patients with COVID-associated sepsis (COVID sepsis) had more thromboembolic complications. Pulmonary embolism was noted in 32% of patients with COVID and 3% of patients with non-COVID sepsis; however, pulmonary embolism of lower severity developed in patients with COVID sepsis than in patients with non-COVID sepsis [7]. A review of medical records of patients admitted to the ICU with a diagnosis of COVID sepsis or sepsis of other etiologies showed that [8] after adjusting for age, body mass index, malignant neoplasms, cardiac and respiratory failure, rheumatological diseases, diabetes, history of hypercoagulability, and incidence of thrombosis, no statistically significant difference was found in the incidence of thrombotic events in patients with COVID compared with patients without COVID. In-hospital death occurred in 35% of patients with COVID sepsis and in 59% of patients with bacterial sepsis [9]. Risk factors for severe and fatal COVID outcomes, as well as dysregulation of the patient's response to infection, leading to sepsis and septic shock, and biomarkers of sepsis have been described in our previous reviews [10–12].

This article reviews studies that described and compared the clinical characteristics and outcomes of patients with

COVID-associated or non-COVID-associated sepsis. The results of such comparisons are of great importance for risk stratification and treatment selection.

PROTEOMIC BIOMARKERS

A retrospective comparison of patients with COVID sepsis admitted to the ICU during the pandemic and patients with sepsis due to carbapenem-resistant *Klebsiella pneumoniae* (CrKP) admitted to the ICU before the pandemic demonstrated a more severe degree of primary lung injury in COVID sepsis; however, milder systemic inflammatory response, lower Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores and better preservation of cardiac, liver, kidney, coagulation, and circulatory functions even in the most severe cases of primary infection were noted when compared with patients with bacterial sepsis [13]. Bacterial infections affect organs faster than the SARS-CoV-2, which increases the SOFA and APACHE II indices [14]. However, immunosuppression in patients with COVID is more severe, manifesting itself in a more severe leukopenia [13]. The proportion of patients with COVID sepsis receiving extracorporeal membrane oxygenation (ECMO) was higher than that of patients with bacterial sepsis (6.5% vs. 0%, respectively). In viral sepsis, hospital mortality is lower (12% vs. 40%), and the duration of intensive care is shorter (6.5 vs. 23 days). Moreover, lethal outcomes of patients with CrKP-induced sepsis occurred more often in the early stages of hospital stay, and those of patients with COVID-induced sepsis occurred mainly in the later stages. Bacterial sepsis more likely leads to secondary organ damage, including renal dysfunction, requiring systemic blood purification therapy to reduce inflammation and organ damage. Thus, severe COVID has the clinical characteristics of typical sepsis and is comparable to classic bacterial sepsis, although it differs in quantitative indicators [13].

L. Heubner et al. [15] also compared patients admitted in the ICU treated for sepsis who were diagnosed with COVID with patients having sepsis without COVID but obtained different results. The SOFA score at ICU admission (12 points in the COVID group vs 9 points in the non-COVID group) and in-hospital mortality (59% with COVID vs 29% without COVID) were significantly higher in the COVID group. COVID causes severe lung damage; therefore, supportive therapies such as invasive artificial lung ventilation (ALV, 100% vs. 56%), inhaled nitric oxide (35% vs. 2%), and ECMO (28% vs. 5%) are used more often than that in patients with non-COVID sepsis. Coinfection or superinfection was detected in 48% of patients with COVID sepsis, with a particularly high risk of hospital-acquired infection in patients requiring renal replacement therapy (38% with COVID and 29% without COVID). COVID has been identified as an independent risk factor for in-hospital mortality in patients with sepsis. Age, procalcitonin levels >2 ng/mL, need for invasive ALV, renal replacement therapy and ECMO, and septic shock were identified as additional

risk factors for in-hospital mortality. These factors should be considered to identify high-risk patients.

Expression of the multipotent regulatory peptide proadrenomedullin in various tissues and organs is activated by inflammation, hypoxia, and infection. The stable precursor MR-proADM (mid-regional pro-adrenomedullin) is considered a biomarker of endothelial damage and a predictor of multiple organ failure and death in respiratory infections and sepsis. MR-proADM maintains endothelial stability and regulates the endothelial barrier, microcirculation, and vascular permeability. The prognostic value of MR-proADM levels has been established in the context of respiratory infections, sepsis, and septic shock [16, 17].

High MR-proADM levels reflect COVID progression, which enables the identification of patients at the greatest risk of ARDS development and death [18]. G. Montrucchio et al. [19] analyzed more than 200 patients with COVID-associated pneumonia (COVID pneumonia) admitted to the ICU in critical condition and confirmed the statistical significance of MR-proADM as a biomarker of mortality. Plasma MR-proADM concentrations >1.5 nmol/L are an independent risk factor for 28-day mortality, adjusted for age, lactate level upon admission, SOFA and MuLBSTA scores, superinfections, cardiovascular diseases, and respiratory diseases. MR-proADM levels assessed within 48 h of admission were significantly higher in nonsurvivors than in survivors (2.3 vs 1.2 nmol/L, $p < 0.0001$). On days 3 and 7 of the ICU stay, the MR-proADM levels remained correlated with mortality ($p < 0.0001$). Compared with other biomarkers (C-reactive protein [CRP], procalcitonin, lactate dehydrogenase [LDH], D-dimer, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), myoglobin, ferritin, troponin-I, interleukin [IL]-6, neutrophil counts, lymphocyte counts, and natural killer cell counts), the MR-proADM value within 48 h of admission to the ICU predicts 28-day mortality most accurately. The role of general inflammatory biomarkers, which received much attention at the beginning of the pandemic, has significantly diminished considering recent data, as increasing concentrations of cytokines and inflammatory biomarkers appear to be insufficient for accurate prognosis [20–22]. G. Montrucchio et al. [19] asserted that MR-proADM is the best biomarker to determine the risk of death in patients with extremely severe COVID. High concentrations of MR-proADM as disease severity increases determine the additional value of this biomarker in predicting disease outcomes according to other authors who measured it in patients with sepsis and septic shock [23]. Thus, the biomarker of endothelial damage and vascular permeability MR-proADM can guide the selection of more intensive treatment regardless of the causative agent, enable the monitoring of the patient's condition, assess treatment efficiency, and detect possible deterioration early, particularly in the ICU. With a persistent decrease in MR-proADM concentrations, patients can be safely transferred from the ICU to general wards without increasing readmissions and/or mortality [19].

During the progression of sepsis, neutrophils are the first line of innate immune defense against infection. In addition to traditional mechanisms such as phagocytosis or the release of inflammatory cytokines, reactive oxygen species, and other antibacterial substances, activated neutrophils release web-like structures composed of tangled, decondense DNA called neutrophil extracellular traps (NETs) that trap bacteria in the bloodstream. Excessive neutrophil activation and NET release may induce a shift in endothelial cells toward a proinflammatory and procoagulant phenotype. Neutrophils and NETs can also degrade the endothelial glycocalyx (EG) and increase endothelial permeability, contributing to impaired microvasculature, tissue hypoperfusion, and life-threatening organ failure in the late stage of sepsis [24]. The glycocalyx is a membrane consisting of proteoglycans, glycosaminoglycans, and glycoproteins that surround all mammalian cells and is an important regulator of vascular and immune responses. In sepsis, vascular dysfunction causes ARDS, compromising the integrity of blood vessels and promoting increased inflammation and thrombosis. An association was found between circulating levels of glycocalyx cleavage products and organ dysfunction and mortality. EG must maintain capillary microcirculation, adsorption and reabsorption through capillary membranes, and fluid distribution throughout tissues. Immune-mediated degradation of EG increases vascular permeability, microvascular thrombosis, and leukocyte recruitment and leads to sepsis and septic shock. EG damage and circulating concentrations of its degradation products are considered markers of sepsis-induced endothelial dysfunction and contribute to a range of clinical manifestations of sepsis, including acute renal failure (ARF), respiratory failure, coagulopathy, septic cardiomyopathy, and encephalopathy (the latter is characterized by diffuse cerebral dysfunction) [25]. Vascular and immune dysfunction is a distinguishing feature of COVID and a major contributor to clinically registered deterioration. High concentrations of the glycocalyx components syndecan-1 (247 vs. 85 pg/mL) and hyaluronan (26 vs. 3 pg/mL) in the plasma of patients with COVID compared with healthy controls correlate with immune hyperactivation and disease severity. Parallel assessment of markers of glycocalyx degradation and inflammatory cytokines may identify patients at risk of developing severe COVID complications [26].

Massive apoptosis of T lymphocytes and release of NETs affect the accumulation of extracellular chromatin, which is registered in microbial sepsis, is associated with sepsis mortality, and contributes to hyperinflammation, immune dysfunction, coagulopathy, and thrombosis [27]. Degradation and clearance of extracellular chromatin are impaired in severe COVID pneumonia and bacterial sepsis. DNase I inhibitor actin prevents chromatin clearance. Concentrations of extracellular DNA and actin are higher in the plasma of patients with microbial sepsis (all patients with microbial sepsis in the study [27] developed refractory septic shock with multiple organ failure) than in the plasma

of patients with severe COVID pneumonia. In patients with microbial sepsis, high plasma concentrations of actin and extracellular chromatin correlate with thrombophilia and coagulopathy. Proteomic profiling links DNase activity with COVID mortality. Plasma samples with low DNase activity showed higher levels of CRP, procalcitonin, and creatinine, indicating hyperinflammation, bacterial coinfection, and kidney damage, respectively. Low DNase activity was more common in nonsurvivors. Survivors with low plasma DNase activity had poorer recovery of lung function and a 4.2-fold increase in mortality rate. Thus, low DNase activity and extracellular chromatin degradation identify patients at increased risk of death in a cohort with high disease severity [28].

The COVID pandemic has brought increased attention to cellular toll-like receptors (TLRs) because the interaction of the SARS-CoV-2 with these receptors is an important mediator of COVID immunopathogenesis. TLR2, TLR4, TLR7, and TLR8 are important for viral control and immune activation in patients with COVID [29]. TLR signaling pathways, as a component of innate immunity, are significant in viral particle recognition and immune system activation. TLRs and TLR agonists have been widely used in the development of COVID vaccines to induce a strong and long-lasting immune response [30].

TLR activation induces the secretion of proinflammatory cytokines such as IL-1 α , IL-1 β , IL-4 and IL-6, as well as interferons (IFNs), and promotes viral exit [31]. TLRs selectively recognize pathogen-associated molecular patterns (PAMPs) produced by bacteria and viruses that have entered the body and damage-associated molecular patterns (DAMPs) released by damaged cells. Several DAMPs/PAMPs recognized by TLRs were found in the blood and lungs of patients with critical COVID [29].

TLR3 activation by various RNA viral infections leads to the production of inflammatory cytokines and the antiviral immune response of IFN type I. Low TLR3 expression and high TLR4 expression in peripheral blood cells are associated with poor outcomes in patients with severe COVID [32]. TLR3 and TLR7 are involved in the control of innate immunity during pulmonary infection with SARS-CoV-2. Overexpression of TLR3, TLR7, TLR8, and TLR9 was registered in the nasopharynx of patients with COVID. This finding can be used to assess the severity of the condition of patients with COVID. Inhibition of histamine-induced TLR3 expression in SARS-CoV-2-infected cells leads to improved outcomes in patients with COVID [33].

Genetic background influences morbidity and mortality in patients with COVID. As with severe bacterial infection, patients with severe COVID develop typical symptoms of sepsis (shock, microcirculatory dysfunction, and dysfunction of multiple organs). TLR polymorphisms influence changes in human immune responses to infections. Genetic analysis of the functional variants of TLR3 showed that a mutation in exon 4 (rs3775291) of TLR3 disrupt receptor expression and the subsequent signaling cascade. This may explain

why some people are susceptible to SARS-CoV-2 infection. *TLR3* (rs3775290) and *TLR7* (rs179008) polymorphisms are associated with an increased risk of COVID pneumonia; the *TLR3* polymorphism L412F causes a high risk of severe COVID [34]. The interaction of TLR4 with the viral spike protein activates the expression of inflammatory cytokines and may cause the development of viral sepsis after SARS-CoV-2 infection. Minor alleles of the *TLR4* genes 299Gly (G) and 399Ile (T) are associated with COVID severity, cytokine storm, and mortality. Rare *TLR7* mutations are associated with impaired responses of IFN types I (IFN- α , IFN- β , and IFN- ω) and II (IFN- γ) and increase the risk of severe COVID development. Immune cells from patients with abnormal TLR7 function show little response to SARS-CoV-2 and produce small amounts of IFN [29].

TLR hyperactivation is a key molecular mechanism of bacterial sepsis [35]. In the pathogenesis of systemic infections caused by Gram-positive and Gram-negative bacteria, phagocytic cells, namely, monocytes and macrophages, which recognize PAMPs of invading bacteria through TLRs, played an important role. Lipopolysaccharide, the main component of the cell wall of Gram-negative bacteria, interacts with TLR4, inducing the transcriptional activation of proinflammatory cytokines. Long-term exposure to lipopolysaccharide induces a state of immunosuppression called endotoxin tolerance, which reprograms TLR-mediated inflammatory responses, resulting in decreased production of proinflammatory cytokines. Similar to lipopolysaccharides, cell wall components of Gram-positive bacteria can induce a tolerant state in monocytes through the activation of the TLR1/TLR2 or TLR2/TLR6 signaling pathways. The tolerant state of monocytes with a reduced ability to produce proinflammatory cytokines in patients with sepsis and septic shock is the most characteristic sign of septic immunosuppression, which is associated with increased mortality and occurrence of secondary foci of nosocomial infections caused by weakening of inflammatory reactions after repeated contact with the pathogen. Reduced expression of HLA-DR on the cell surface is a surrogate marker of the refractory state of monocytes during sepsis [36]. Patients with severe respiratory failure caused by SARS-CoV-2 have reduced expression levels of HLA-DR on the cell membranes of circulating monocytes. A unique immune dysregulation in which, despite suppression of HLA-DR expression, monocytes are still producing the proinflammatory cytokines TNF- α and IL-6 distinguishes patients with critical COVID from patients with bacterial sepsis [37].

During severe acute infections such as sepsis and COVID, hyperactivated neutrophils release cytotoxic molecules. Although such inflammatory mediators are necessary to control the infectious process, their excessive production damages healthy cells. Inappropriate neutrophil stimulation during systemic inflammation is associated with increased mortality. Therefore, neutrophil function must be controlled to effectively kill microorganisms with minimal harm to the human

body. Leukocyte activation in response to microbial stimuli is regulated by the density of sialic acid in the glycocalyx. By binding to TLR4, lipopolysaccharide activates the membrane-bound neuraminidase of macrophages and dendritic cells and induces an immune response. The combined activity of microbial and endogenous neuraminidases hydrolyzes sialic acid with subsequent neutrophil hyperstimulation. In clinically relevant models of sepsis caused by peritonitis or pneumonia, inhibition of overactivated neuraminidase prevents massive neutrophil infiltration into the lung tissue, significantly increasing the survival of septic mice infected with *Klebsiella pneumoniae* [38]. Similar to bacterial sepsis, during severe SARS-CoV-2 infection, neutrophils support hyperinflammation, which is associated with poor prognosis. In severe COVID, endogenous neuraminidase is expressed at high levels in the neutrophil-infiltrated airways. Treatment of whole blood from patients with severe COVID with the neuraminidase inhibitors oseltamivir or zanamivir (the drug is not registered in the State Register of Medicines) suppresses the hydrolysis of sialic acid and reduces neutrophil infiltration in the lungs, viral load, and lung damage. The inclusion of oseltamivir in combination therapy prevents the hyperactivation of neutrophils while maintaining their microbicidal ability, stops the progression of COVID, and reduces the risk of death in patients with severe disease [39].

The cytokine storm that often accompanies COVID potentially causes tissue and organ damage and is associated with worse outcomes. Patients with bacterial sepsis also have excessive cytokine release with systemic hyperinflammation; however, this is followed within 24 h by an immunosuppressive phase, compensatory anti-inflammatory response syndrome (CARS), so-called immune paralysis, limiting organ damage. In this condition, the immune system response to the primary infection is suppressed, which is accompanied by increased susceptibility to secondary infections, causing a large number of deaths in the late stage of sepsis. Proposed causes of CARS include apoptosis of dendritic cells, B cells, CD4 and CD8 T cells, and an increase in the proportion of regulatory T cells (Tregs), which are less vulnerable to sepsis-induced apoptosis. Tregs enhance the anti-inflammatory response, causing a shift from an initial proinflammatory response to an anti-inflammatory immune response. The relative increase in Treg counts further contributes to immunosuppression in sepsis, including the suppression of lymphocyte, macrophage, and dendritic cell functions [3]. Lymphopenia and granulocytosis are less severe, and the concentrations of the cytokines IL-2, IFN- γ , and TNF- α are significantly increased in the blood of patients with COVID-associated ARDS (COVID ARDS) compared with patients with bacterial sepsis. This fundamental difference in immune competence between patients with COVID ARDS and those with bacterial sepsis may have implications for the personalized selection of immunosuppressive or step-up therapy [14].

(Clara cell 16 kDa protein (CC16), also known as uteroglobin, is expressed in lung epithelial club cells (Clara cells) and exhibits anti-inflammatory and immunomodulatory properties in lung diseases. CC16 concentrations are significantly increased in the serum of patients with severe COVID and patients with severe sepsis of extrapulmonary origin compared with healthy controls, with no significant differences between infections with and without pulmonary origin. The authors [40] believe that high serum concentrations of CC16 in both severe forms of COVID and sepsis are biomarkers of epithelial cell damage in pulmonary and nonpulmonary infectious diseases.

Angiotensin-converting enzyme 2 (ACE2) is the functional cellular receptor for endocytosis of SARS-CoV-2. Circulating levels of ACE2 are generally low (<17 mU/L); however, serum levels of patients with critical COVID are significantly higher than those of patients with severe COVID (54 vs. 34.5 mU/L; $p < 0.0001$) and patients with severe sepsis without COVID (41 mU/L; $p < 0.03$) regardless of concomitant diseases. In patients with critical COVID, circulating ACE2 activity upon hospital admission correlates with inflammatory biomarkers and is further increased during the hospital stay. The SOFA score was 3–8 points in patients with severe COVID, 10–13 in patients with extremely severe COVID, and 5–11 in patients with critical COVID and sepsis. ARDS developed in all these patients. Most patients who died of COVID experienced a significant increase in ACE2 activity before death compared with survivors, whereas no significant changes in ACE2 activity were registered in survivors before hospital discharge. High ACE2 activity (≥ 45.4 mU/L) predicted a higher 30-day mortality rate (65% vs. 37%, $p < 0.0001$). The authors [41] concluded that serum ACE2 is a nonspecific biomarker of systemic inflammation because its level in the circulation increases in severe sepsis, which predicts the disease course and mortality.

Sepsis, septic shock, and COVID induce dynamic changes in the immune system that are promising candidates for new biomarkers to improve diagnostic accuracy and patient stratification, for example, increased levels of the peptide hormone hepcidin (a systemic regulator of iron metabolism) and the acute phase inflammatory reactant ferritin (a protein, which binds free iron). Serum ferritin is released from damaged cells during inflammatory conditions. To compare the prognostic ability of hepcidin and ferritin for different diagnoses, patients with severe COVID, septic shock, and sterile inflammation after joint replacement were examined [42]. Comparison of patients with healthy donors showed that hepcidin levels increase sharply during infections, including those causing sepsis, reflecting the activation of immune cells because of internal stimuli without the direct involvement of the infectious agent, whereas ferritin levels are increased 4 times during septic shock caused by pathogens (bacterial, fungal, and parasitic) and by 6 times in case of COVID, compared with sterile inflammation. The results confirm that hepcidin and ferritin are markers of

septic shock and other pathologies associated with acute inflammation. Moreover, hepcidin and the ratio of hepcidin to ferritin (higher in survivors) are predictors of 28-day mortality only in septic shock but not in COVID [42].

Pentraxin-3 (PTX3), a marker of microvascular inflammation, is an acute phase protein. It is a component of innate humoral immunity that is released by several cell types in response to infection or tissue damage. Circulating PTX3 concentrations are abnormally increased (>2 ng/mL) in all patients with severe sepsis or septic shock, which is associated with disease severity, multiple organ failure, and lethal outcomes [43].

More than half of the patients with severe COVID had sepsis of pulmonary origin, which met the definition of sepsis according to the criteria of the third international consensus “Sepsis-3” [44]. Patients with COVID tend to have high plasma PTX3 concentrations (particularly those who do not survive 28 days, 30 vs 18 ng/mL); however, these are lower than those in patients with non-COVID pulmonary sepsis on days 1, 2, and 7 and upon discharge from the ICU. The role of inflammation in COVID pathogenesis remains controversial. Circulating levels of many proinflammatory cytokines are significantly higher in patients with COVID than in healthy individuals; however, even in patients with severe COVID, circulating levels of proinflammatory cytokines are usually not higher than those in patients with systemic inflammatory syndrome [43]. For example, in a meta-analysis of 37 studies [45], the average level of circulating IL-6, which is considered the main mediator of the cytokine storm, was 55 pg/mL in patients with COVID in critical condition, 460 pg/mL in patients with ARDS without COVID, 984 pg/mL in patients with sepsis, and 3111 pg/mL in patients with cytokine release syndrome. In this regard, some authors have proposed downgrading the term “cytokine storm” in COVID to “cytokine rain” because circulating levels of proinflammatory cytokines (IL-6, IL-8, and TNF) are only a fraction of the concentrations reported in bacterial sepsis/septic shock [46]. The transfer of stereotypes (e.g., “cytokine storm”) from one nosological entity to another should be avoided [47]. The initial circulating PTX3 concentration (20 ng/mL) was similar in patients with COVID whose condition met or did not meet the diagnostic criteria for pulmonary sepsis. It was elevated to a lesser extent in patients with COVID than in patients with sepsis or septic shock without COVID (20 vs 30 ng/mL). This result may indicate a different origin of infection (more often bacterial in patients with sepsis) or a different role of PTX3 in the pathogenesis of the two syndromes. However, based on the evidence set, immune suppression in COVID may be more common. This is significant because both hyperinflammation and immune suppression are considered therapeutic targets for COVID [43].

In patients with severe COVID and those with sepsis, the levels of cytokines IL-6, amphiregulin (AREG), and growth differentiation factor 15 (GDF-15), which are associated with disease severity and prognosis, were measured. The median

indices on the APACHE II and SOFA scales in patients with COVID and sepsis were 14 and 21 points ($p < 0.01$) and 5 and 9 points ($p < 0.01$), respectively. AREG is a member of the epidermal growth factor family of factors, and GDF-15 is part of the transforming growth factor β (TGF- β) family of factors. Concentrations of the cytokines IL-6, AREG, and GDF-15 are increased in all patients, but more significantly in sepsis than in COVID [48].

In a multicenter study [49] involving 13,781 inpatients with COVID and confirmed (2.5%), suspected (46%), or absent (51.5%) community-acquired bacterial coinfection, bacterial coinfection was significantly more common in patients with a neutrophil-to-lymphocyte ratio of ≥ 15 ($p < 0.001$) in the first 48 h after hospitalization. Bacterial coinfection confers the greatest risk of ICU admission, need for ALV, and in-hospital mortality ($p < 0.001$ for all cases) among other known risk factors for severe disease. The mortality rate for bacterial coinfection in patients with COVID (24%) is similar for SARS-CoV-2 alpha, delta, and omicron variants and is significantly higher than that in patients with community-acquired bacteremia hospitalized before the COVID pandemic (5.9%; $n=99,170$). The authors concluded that a high neutrophil-to-lymphocyte ratio within 48 h of patient hospitalization is a predictive indicator of bacterial coinfection with COVID [49].

Phenotyping is increasingly being used to better understand the heterogeneity of an infectious disease and can provide prognostic information. In 63,858 patients with non-COVID sepsis defined by Sepsis-3 criteria from three observational cohorts, four clinical phenotypes (α , β , γ , and δ) were identified with different outcomes and treatment responses. A prospective cohort study of pneumonia-induced sepsis ($n=583$) and three clinical trials on sepsis ($n=4737$) established the reproducibility of the identified phenotypes and their correlation with biological parameters and clinical outcomes. Mortality within 28 days was 5% for the α phenotype, 13% for the β phenotype, 24% for the γ phenotype, and 40% for the δ phenotype. Across all cohorts and trials, 28- and 365-day mortality rates were the highest in patients with the δ phenotype ($p < 0.001$ compared with other phenotypes), which has characteristics similar to the hyperinflammatory phenotype. Levels of coagulation markers (thrombin-antithrombin complex, plasminogen activator inhibitor 1, and D-dimer) were significantly higher in the δ phenotype than in others. The highest levels of the endothelial dysfunction markers intercellular adhesion molecule 1 (ICAM-1) and E-selectin were noted in the γ -phenotype, and those of vascular cell adhesion molecule 1 (VCAM-1) were registered in the δ -phenotype. Phenotypes are multidimensional and cannot be described solely by disease severity, pattern of organ dysfunction, or location of infection; however, they are correlated with patterns of immune response [50]. Because severe COVID meets the criteria for sepsis, N. Bruse et al. [51] applied these phenotypes to 10,884 patients hospitalized for

COVID sepsis. In general, the characteristics and mortality associated with COVID sepsis phenotypes are similar to those described by C.W. Seymour et al. [50], with the α -phenotype demonstrating the most favorable outcome, whereas the δ -phenotype had the highest mortality. The α -phenotype has the lowest APACHE IV score, the δ -phenotype has the highest score, and the γ -phenotype is between these extremes. Interestingly, after treatment with dexamethasone as standard therapy for COVID, a significantly higher proportion of patients with COVID admitted to the ICU exhibited the δ phenotype (6% before dexamethasone therapy vs. 11% after it, $p < 0.001$), whereas the survival rate of patients with this phenotype was better than the cohort without dexamethasone therapy. The administration of dexamethasone (often before ICU admission) could lead to a modification of the phenotype *per se*. The administration of dexamethasone, and later tocilizumab (not registered in the State Register of Medicines), appeared to improve the outcomes in patients with the δ -phenotype (mortality rate, 60% vs. 41%, $p < 0.001$) because it has the highest concentrations of IL-6 and TNF [51].

The endothelium is involved in the development of macrocirculatory and microcirculatory disorders and organ dysfunction in patients with serious infections in the ICU. Endothelial damage and dysfunction play a damaging role in the pathogenesis of infections, and endothelial-associated molecules are potential diagnostic and/or prognostic biomarkers of infection. S. Kaur et al. [52] examined biomarkers of endothelial damage as predictors of death in the ICU in patients with hepatic cirrhosis and severe COVID and patients with hepatic cirrhosis and bacterial sepsis. The levels of endothelial biomarkers did not differ significantly among patients with hepatic cirrhosis of different groups. ICAM-1 levels correlate with the SOFA and chronic liver failure-organ failure (CLIF-OF) indices and independently predict lethal outcomes in these patients with an odds ratio of 3.24 and an area under the receiver operating characteristic curve (AUC) (a characteristic of the classification quality; the higher the AUC value, the more accurate the classification model) of 0.74. The 28-day survival rate was 73% in patients with severe COVID, 27% in those with severe COVID and hepatic cirrhosis, and only 20% in those with sepsis and hepatic cirrhosis. In patients with hepatic cirrhosis and sepsis, mortality was caused by severe sepsis or septic shock with progressive liver or multiple organ failure. The addition of ICAM-1 to the combined model for end-stage liver disease (MELD model) was 10% more accurate in predicting short-term mortality compared with the MELD score in both groups of patients with hepatic cirrhosis, highlighting endothelial damage as a critical prognostic factor in these patients. The endothelium is not the only component of the human response to infection; however, it is a key factor supporting inflammation and coagulation, leading to microvascular occlusion, hypoxia, and organ dysfunction. Increased expression of ICAM-1 on

activated endothelial cells promotes neutrophil adhesion and migration into tissues during inflammation. The authors registered a significant correlation between high ICAM-1 levels and the severity of organ failure (as measured by SOFA and CLIF-OF indices) [52].

Lactate is an important substrate for the mitochondria in the muscle, heart, and brain during physical activity and is considered a marker of tissue hypoxia. High blood lactate levels are strongly associated with mortality in patients with sepsis and septic shock; apparently, it is not directly related to tissue hypoxia but reflects mitochondrial dysfunction and high adrenergic stimulation. U.W. Iepson et al. [53] concluded that in sepsis, hyperlactatemia is associated with a poor outcome but is not its cause, and tissue hypoxia is a predictor of a poor outcome independent of hyperlactatemia. The main source of lactate in sepsis is a population of immune cells that are mobilized during inflammatory response. This explains why significant amounts of lactate are released from the lungs when sepsis is complicated by ARDS, which is characterized by the accumulation of neutrophils and macrophages. In patients with severe COVID, blood lactate levels are usually nearly normal (< 2.5 mmol/L), indicating preserved mitochondrial function despite systemic hyperinflammation and profound hypoxemia. However, plasma levels of LDH, which controls lactate formation, are and correlate with disease severity and mortality in severe COVID. The origin of LDH is not well understood in COVID. Presumably, it may be associated with damage to alveolar cells. The question of why blood lactate levels do not increase in patients with COVID, who typically have extremely high respiratory rates in response to hypoxemia and systemic hyperinflammation, as in sepsis, remains unanswered. This may be due to the high oxidative metabolism of lactate, which is used as an energy source by the respiratory muscles.

Bacterial sepsis and COVID are associated with the activation of coagulation, which manifests as thrombosis in COVID and as disseminated intravascular coagulation (DIC). High levels of D-dimer (a marker of fibrin dissolution) in the plasma of patients with COVID are associated with disease severity, thrombosis, and mortality. In the plasma of patients hospitalized for COVID (particularly in the ICU), D-dimer levels are significantly lower, and circulating levels of extracellular vesicle expressing tissue factor (EVTF) and the active form of PAI-1 are significantly higher than in patients with sepsis. In sepsis, PAI-1 concentrations are associated with all-cause mortality. High levels of active PAI-1 in patients with COVID limit plasmin degradation of cross-linked fibrin and D-dimer release. This may explain the lower D-dimer levels in patients with COVID than in patients with sepsis. The authors hypothesize that these combined changes create an environment in patients with COVID that promotes thrombosis rather than DIC because of the simultaneous activation of coagulation and inhibition of fibrinolysis. In patients with sepsis, circulating EVTF activates the coagulation system, and PAI-1 inhibits the fibrinolytic system to a lesser extent

than in patients with COVID, leading to higher D-dimer levels and an environment favorable to DIC syndrome rather than thrombosis [54].

A meta-analysis [55] showed that most patients with severe COVID (78%) met the Sepsis-3 criteria for sepsis/septic shock with ARDS. In COVID, ARDS is controversial because the extent to which ARDS caused by SARS-CoV-2 is comparable or different from bacterial ARDS. Both forms of ARDS are accompanied by decreased lung compliance, inflammation, hypoxemia, hypercapnia, and endothelial damage. COVID ARDS is characterized by severe alveolar thrombosis, accompanied by excessive fibroproliferative remodeling of the lung tissue [56]. The phenomenon of respiratory failure in COVID, not registered in ARDS of other etiologies, is "silent hypoxemia" (critically low pO_2 level with mild shortness of breath). Coagulopathy is common in both diseases; however, the coagulation abnormalities caused by COVID are different from the typical DIC noted in bacterial sepsis. Patients with severe COVID often exhibit signs of hypercoagulability, namely, high circulating D-dimer concentrations, high fibrinogen levels, increased prothrombin time, activated partial thromboplastin time, and thrombocytopenia. D-dimer concentrations in patients with severe COVID are consistently higher than those in patients admitted in the ICU and in patients with severe non-COVID pneumonia. "Silent hypoxemia" is life-threatening because it delays timely treatment and contributes to multiple organ failure [47].

F.M. Trovato et al. [57] identified an immunometabolic signature in plasma mononuclear cells, serum, and blood of patients with COVID sepsis and sepsis of other etiologies in 10 days of critical illness. Choline metabolism is of interest because macrophage polarization in response to pathogens requires increased choline uptake to form phosphatidylcholines, which promote cytokine secretion. In patients with COVID, the phosphatidylcholine level increased with an increase in disease severity on the SOFA scale; however, this trend was not registered in patients with sepsis without COVID.

Concentrations of the inflammatory cytokines IL-6, IL-1 β , and TNF- α are increased in patients with COVID compared with healthy controls, with no difference from sepsis of other etiologies. In contrast, IFN- α levels are increased in COVID compared with healthy controls and sepsis. In patients with COVID, T cells and monocytes express high levels of the immune checkpoints programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1), with PD-L1 expression correlating with plasma levels of IFN- γ , a key component of the innate antiviral response. The COVID immunometabolic signature links PD-L1 and IFN- γ expression by monocytes and T cells with systemic metabolism. The inflammatory response results in the loss of essential circulating nutrients (lipids and amino acids) and increased mitochondrial dysfunction in immune cells, with an increase in the glycolysis rate and use of glucose as a substrate for energy production.

Increased expression of PD-L1 on monocytes and T cells correlates with decreased tryptophan levels, indicating a connection between key components of immunometabolism. The depletion of tryptophan, a T-cell metabolic factor, negatively correlates with IL-6 and IFN- γ concentrations, as well as SOFA, and is one of the main mechanisms of resistance to immunotherapy, which leads to anergy and apoptosis of T cells. This is reflected in high kynurenine levels and a high kynurenine/tryptophan ratio in most severe COVID compared with sepsis. Kynurenine is an intermediate product of tryptophan enzymatic disintegration in the liver. Together with glutamine, leucine, and phenylalanine, it is part of a group of metabolites that can distinguish COVID from sepsis. Glutamine levels are higher in patients with COVID than in patients with sepsis of other etiologies. This amino acid is used as a major respiratory substrate by glutaminase-expressing tissues, including the liver, kidney, intestine, lymphocytes, and monocytes. Decreased glutamine levels have a harmful effect on monocyte function. In sepsis, glutamine synthetase activity increases in the skeletal muscle, which depletes glutamine resources. Its use as a dietary supplement in patients with critical illness resulted in the decreased production of inflammatory cytokines and increased IFN- α -associated immune response. Thus, patients with COVID exhibit a plasma metabolic pattern different from that in patients with sepsis of other causes [57].

The striking similarities between bacterial sepsis and COVID are their long-term effects. In both groups of patients [58], hospital discharge did not mean complete recovery and was often accompanied by long-term disabling consequences. In bacterial sepsis, a group of complications after discharge is called persistent inflammation, immunosuppression, and catabolism syndrome (PICS), whereas in patients with SARS-CoV-2 infection, it is known as "long COVID," or post-COVID syndrome. Long COVID is not much different from PICS. The most common persistent symptoms are fatigue, muscle pain, poor sleep, and cardiac and cognitive impairment [58]. In contrast to PICS, long COVID is often diagnosed in patients with mild acute SARS-CoV-2 infection (without hospitalization) [59]. The presence of a "long phenotype" in both diseases convincingly indicates severe and long-term deregulation of immune-inflammatory responses (with obvious signs of immunosuppression) and organ homeostasis. COVID in hospitalized patients should be considered viral sepsis [47].

The urokinase plasminogen activator (uPA) system is involved in inflammation, fibrinolysis, cell proliferation, migration, and adhesion. The binding of uPA to its receptor (uPAR) activates the proteolytic cascade that converts plasminogen to plasmin. The soluble form of suPAR is considered a biomarker of inflammation, immune activation, and inhibition of fibrinolysis; its concentrations increase in some systemic diseases, including sepsis. Serum suPAR levels were measured in patients with severe COVID and patients with pulmonary sepsis without COVID within 6 h

of ICU admission. Patients with COVID had higher levels of suPAR than patients with sepsis without COVID. In patients with severe COVID, suPAR is positively correlated with LDH, D-dimer, ferritin, CRP, age, and APACHE II score. In patients who were subsequently intubated, high suPAR levels on admission correlated with ALV duration. In patients with non-COVID sepsis, suPAR levels correlate with age and APACHE II score. The predictive value of suPAR on AUC in early COVID (within 24 h of hospitalization) for the risk of death was 0.81 with a threshold value of 6.3 ng/mL ($p < 0.0001$). In contrast, suPAR measured at the time of diagnosis of non-COVID sepsis does not distinguish patients who will survive from those who will not and does not appear to be a predictive factor of mortality [60].

Metabolic dysfunction contributes to increased mortality in patients with COVID. Metabolomic analysis of plasma and comparison of the metabolic profiles of patients with asymptomatic, moderate, and severe COVID with those of healthy controls [61] revealed significant changes in the levels of metabolites, particularly arachidonic and linolenic acid metabolites. In asymptomatic patients, the biosynthesis of arginine and metabolism of alanine, aspartate, and glutamate are significantly impaired. When metabolites were compared between groups, high concentrations of L-citrulline and L-glutamine were registered in asymptomatic carriers of SARS-CoV-2 as well as in patients with moderate-to-severe COVID at the convalescent stage. An experimental model showed that combination therapy with L-citrulline and L-glutamine effectively protects against coronavirus infection and endotoxin-induced sepsis and prevents pulmonary fibrosis and damage to the central nervous system. These findings may form the basis of a new strategy for the treatment of infections, including COVID and sepsis [61].

During SARS-CoV-2 infection, innate immune cells produce various inflammatory cytokines; however, only the combination of TNF- α and IFN- γ induces inflammatory cell death, so-called PANoptosis, a unique pathway of programmed cell death through the activation of the STAT1/IRF1 (signal transducer and activator of transcription 1/interferon regulatory factor 1) signaling pathway. *NOS2*, one of the genes whose activity is regulated by this signaling axis, encodes inducible nitric oxide synthase (iNOS). STAT1/IRF1 signaling activates *NOS2* in patients with severe and extremely severe COVID and regulates iNOS expression to produce nitric oxide (NO) from arginine, which causes inflammatory cell death in response to the coactivation of TNF- α and IFN- γ . TNF- α and IFN- γ induce synergistically iNOS expression and NO production more than either alone. Excessive NO production leads to lung damage because of the formation of toxic oxidants. Although cytokine storm is a key component of the pathology of sepsis in the early stages of the disease, arginine levels are higher in COVID ARDS than in ARDS caused by bacterial sepsis. Arginine depletion strategies that block its conversion to NO effectively inhibit viral replication [56]. The inhibition of PANoptosis by neutralizing antibodies against

TNF- α and IFN- γ reduces mortality in cytokine storm disease models, including COVID and sepsis [62].

Acute respiratory distress syndrome is a form of severe hypoxic respiratory failure with inflammatory damage to the alveolar–capillary barrier and extravasation of protein-rich edematous fluid into the airspace. Patients with ARDS are at risk of complications such as thrombosis, pulmonary fibrosis, and ARF. Although many treatments for ARDS have been investigated over the past decades, >100 clinical trials have failed to produce positive results [63]. Maintenance therapy remains the mainstay of treatment because of both the multisystem involvement and the high heterogeneity of this condition. COVID ARDS and non-COVID ARDS have similar pathological features and clinical manifestations, with COVID ARDS characterized by a longer-lasting hyperinflammatory state, longer-lasting respiratory failure, and a higher incidence of thrombosis. A comparison study of biochemical changes in the blood during ARDS of different etiologies identified several hundred molecules related to various biological processes, whose expression differs in patients of these two groups [56].

R. Batra et al. [56] established that 12 signaling proteins (including effectors of the JAK/STAT signaling pathway—proteins IL-6RA, IL-7, and PDGFs A and B) are expressed at higher levels in COVID ARDS than in ARDS caused by bacterial sepsis, and 6 proteins (GH, IL-10, IL-2RA, LIF, OSM, and THPO) are expressed at lower levels. Clinical trials have shown improved outcomes in patients with COVID treated with JAK protein kinase inhibitors [64, 65]. When comparing omic associations with clinical manifestations (ARF, thrombocytosis, $\text{PaO}_2/\text{FiO}_2$, and mortality), 249 ARF-associated molecules were identified in the two ARDS groups, and 111 molecules were associated with platelet count. Moreover, 76 molecules overlapped in the two ARDS groups, namely, 49 molecules in the ARF signature and 27 molecules in the thrombocytosis signature. A multicenter study [66] revealed an increased incidence of thrombotic complications (mainly pulmonary embolism) in patients with COVID ARDS compared with patients with non-COVID ARDS (12% vs. 2%, $p < 0.01$).

Moreover, 37% of patients with COVID ARDS and 62.5% with bacterial sepsis and ARDS had ARF. ARF-associated metabolites belong to two main groups: amino acids and acylcarnitines. Amino acids and acylcarnitines are involved in mitochondrial bioenergetic processes. Mitochondrial dysfunction often results in oxidative stress, which is a characteristic sign of ARDS of any etiology. Therefore, impaired metabolism of acylcarnitines and amino acids is consistent with widespread mitochondrial dysfunction in ARDS associated with ARF [56].

In an extended study comparing ARDS of different etiologies based on blood analysis [56], the same group of researchers performed a similar analysis of metabolomic and proteomic profiles of urine samples from patients with bacterial sepsis-induced ARDS and COVID ARDS, correlating them with clinical

manifestations [67]. A proteomic signature of lethality has been identified, which contains proteins associated with ARDS pathogenesis, including cell adhesion/extracellular matrix molecules (CAM/EMM), inflammation, coagulopathy, and mitochondrial dysfunction. The best metabolic signals include tiglylcarnitine (acylcarnitine representing mitochondrial function) and glycoprotein 6 (GP6, a collagen receptor, a risk factor for venous thromboembolism, which is involved in EMM signaling and platelet activation). For the functional interpretation of differentially expressed molecules, a network of molecular interactions was constructed, in which other acylcarnitines are located near tiglylcarnitine, the level of which is increased in COVID ARDS compared with ARDS caused by bacterial sepsis. The GP6 network environment consists of EMM- or CAM-associated proteins with increased expression in COVID ARDS compared with that in bacterial ARDS. Within the network, cross-links exist between the CAM/EMM clusters and group of acylcarnitines, mediated by a group of inflammatory proteins monocyte chemoattractant protein. In COVID ARDS, ARF-associated 10 molecules (8 metabolites and 2 proteins), 6 metabolites associated with $\text{PaO}_2/\text{FiO}_2$, and 61 molecules (1 metabolite and 60 proteins) associated with mortality were detected; no molecules were associated with platelet count. In ARDS caused by bacterial sepsis, no significant associations with any clinical manifestations were observed.

Biomarkers of pathological processes associated with ARDS, including inflammation, renal dysfunction, and pulmonary hypertension are the most differentially expressed proteins that constitute the lethality signature. For example, the NT-proBNP level in the urine indicates pulmonary hypertension, IGFBP-2 is also an indicator of pulmonary arterial hypertension, FABP4 is considered a marker of glomerular damage, CXCL16 is a marker of adverse outcome in diabetic nephropathy, and VEGFA contributes to increased inflammation in severe COVID. Notably, proteins associated with mortality were not detected in plasma samples collected from the same patients with COVID ARDS [56]. The results obtained indicate significant molecular differences in patients with ARDS of various etiologies and the synergism of EMM molecules, inflammation, and mitochondrial dysfunction in the pathogenesis of ARDS. Multiomic co-expression network analysis in ARDS revealed an inflammatory protein-mediated association between CAM/EMM and mitochondrial dysfunction represented by acylcarnitines. This connection highlights the synergy between different cellular processes in ARDS [67].

TRANSCRIPTOME BIOMARKERS AND MODELS

Based on gene expression in the blood, a classifier of the severity of viral infections, including COVID, has been developed [1]. For this purpose, six mRNAs (the expression of *HK3*, *DEFA4*, *BATF* are increased, and the expression of *HLA-DPB1*, *LY86*, and *TGFBI* are decreased) of the

human immune response were selected from the data of 21 transcriptomic clinical studies of viral diseases. To distinguish between patients with severe and nonsevere infection, the 6-mRNA classifier has an AUC of 0.94; to identify patients with severe respiratory failure, the AUC is 0.89; and to predict 30-day mortality in viral diseases, the AUC is 0.90. In the future, the classifier can help determine the level of medical care for patients with COVID and other acute viral infections. The authors of the report [1] note that the assessment using the 6-mRNA classifier predicts severe respiratory failure and death much more accurately than the only analysis that has been approved by the Food and Drug Administration (FDA, USA) for emergency use, namely, measuring IL-6 levels. However, they suggest potential improvements in clinical risk assessment when adding the 6-mRNA score to standard risk predictors. Once included into a rapid analysis, the prognostic assessment using the 6-mRNA classifier is proposed to be used as a tool for triaging patients after a diagnosis of SARS-CoV-2 infection or other viral infections.

MicroRNAs (miRNAs, miRs) are small RNA molecules that target mRNAs for degradation or inhibition of translation. Because of this ability, microRNAs play a key role in the regulation of many biological processes and cellular functions. Over the past decade, these molecules are confirmed to be important participants in the pathogenesis of sepsis. The stability, simple structure, and expression of microRNAs in the blood and other biological fluids make them promising sepsis biomarkers and therapeutic targets. Sepsis is characterized by early immune hyperactivation and late immunosuppression. Accordingly, microRNAs with anti-inflammatory activity may be beneficial in early sepsis but harmful in late sepsis. In contrast, miRNAs with proinflammatory activity may be harmful in early sepsis but beneficial in late sepsis. Infection and stress modulate the expression of these molecules. miR-150 is a sepsis-associated microRNA [5]. To suppress lipopolysaccharide-induced apoptosis of macrophages, monocytes, and endothelial cells, miR-150 inhibits the expression of transcription factors, cytokines and adhesion molecules [3] and the expansion and immunosuppressive function of myeloid-derived suppressor cells whose proliferation is associated with multiple organ failure and mortality with sepsis [68] and with innate immune dysfunction in COVID [69]. Levels of circulating miR-150 are reduced not only in sepsis but also in COVID-induced multiple organ failure [70, 71]. The same direction of changes in miR-150 expression in sepsis and severe COVID suggests overlapping molecular pathogenesis.

Sepsis and COVID are highly dynamic diseases; therefore, a deep, comprehensive understanding of their evolution requires analyses at more than one point in time. For this purpose, gene expression trajectories were compared [72] between patients with severe COVID and those with severe sepsis without COVID. Upon ICU admission, patients with COVID exhibited enhanced

antiviral responses and suppressed heme metabolism compared with patients without COVID. Patients with and without COVID differed in the expression of 1215 genes on the day of ICU admission and became clearly similar on day 7, reducing the number of differentially expressed genes to nine, namely, *HES4*, *KLHDC7B*, *KLHDC7B-DT*, *OTOF*, *OR2B6*, *IFI27*, *SIGLEC1* (strengthening of function or activity), *FAM83A*, and *CNR1* (suppression of function or activity). A set of differentially expressed genes is enriched in antiviral response pathways, including “ISG15 antiviral mechanism,” “INF signaling,” “IFN- γ signaling,” and “IFN- α/β signaling,” which were upregulated on the day of ICU admission in patients with COVID sepsis compared with those with sepsis without COVID. On day 7, no significant difference in the representation of any pathways or gene sets was found between the two groups. Thus, the contribution of COVID status to gene expression changes decreased after a week in the ICU if patients with COVID and sepsis and those without COVID became nearly indistinguishable in terms of gene transcription. This coincided with a decrease in the expression of antiviral immunity genes and a relative increase in the expression of heme metabolism genes in patients with COVID sepsis. It reached levels of expression registered in patients with non-COVID sepsis. These results highlight the importance of early antiviral treatment for COVID and the potential of heme-related and immunomodulatory therapies for both diseases to treat general immune dysfunction [72].

Comparison with healthy controls revealed [72] at both time points in the groups of patients with sepsis with or without COVID, the activation of immune pathways, including “neutrophil degranulation,” “IL-1 signaling,” “inflammatory response,” “signaling IL-6/JAK/STAT3,” “complement,” and “TNF- α signaling through NF- κ B.” The “glycolysis,” “coagulation,” and “platelet degranulation” pathways, which are closely associated with both sepsis and COVID, were also activated at both time points in both COVID and non-COVID groups compared with healthy control groups, which highlights the common mechanisms of further dysfunction. Antiviral pathways and gene sets were downregulated over time only in patients with COVID. Conversely, the “heme Biosynthesis” and “heme metabolism” pathways, processes associated with erythroblast maturation and metabolism, showed lower expression in patients with COVID than in those without COVID on day 1, which increased by day 7 until the differences completely disappeared. In contrast, patients without COVID showed increased expression of these genes throughout the disease, which did not change significantly over time. The pathogen-specific response appears to reach its peak early and decline over time. This explains why antiviral therapy for COVID is most effective in the early stages [73], when the virus is the main factor in the disease. Monoclonal antibodies targeting the virus, such as bamlanivimab, casirivimab, and imdevimab, have shown effectiveness in preventing hospitalizations in outpatients [74]

but have demonstrated no differences in patients with severe COVID (at probably later stages of the disease progression) compared with the standard of medical care [75]. Future clinical trials of antiviral drugs against COVID should focus on stratifying patients by disease stage [72].

Heme metabolism was another differentiating factor in patients with sepsis with and without COVID. High expression of heme metabolism genes in patient without COVID may be a compensatory mechanism for hyperinflammation, which does not occur in the early stages of COVID. Although heme metabolism is affected by hypoxia, no significant difference in the PaO₂/FiO₂ ratio was found between the COVID-positive and COVID-negative groups with sepsis. In addition, the hypoxia gene set was activated at both time points in all patients compared with healthy controls. Therefore, the different enrichment of heme metabolic pathways between patients with and without COVID is not due to differences in the degree of hypoxia [72].

The activity of common pathways associated with inflammation decreased over time in all patients. Moreover, in both groups, an increase in the activity of adaptive immune pathways was noted over time. Monitoring changes in gene expression reflecting general immune deregulation indicates the possibility of immunomodulatory therapy for the treatment of both diseases. Two contrasting gene expression trajectories that were noted only in patients with COVID but not in those without COVID patients 1) an early antiviral response, which decreased by day 7, and 2) increased heme metabolism, which reached levels seen in patients with sepsis but without COVID by day 7. Simultaneously, many immune and nonimmune pathways were common to both groups and had similar trajectories. Thus, the predominant pathological processes were extremely similar in the COVID-positive and COVID-negative groups [72]. The results of the above study showed how the gene expression trajectories of severe COVID and sepsis converged after a week in the ICU, which is consistent with the symptomatology and results of biomarker studies [76], which suggest that severe COVID is a form of viral sepsis. The attenuation of antiviral pathway activity over time is consistent with the rapid decline in IFN response in the COVID-positive group [77]. This finding supports the hypothesis that the abnormal immune response rather than the infection itself leads to symptoms, organ damage, and death.

Thus, many cases of severe COVID are probably due to virus-associated sepsis. This hypothesis is supported by the observation that severe COVID exhibits signs of immune dysfunction typical of sepsis (hyperactive inflammatory response and persistent immunosuppression) [78], including increased cytokine expression and T-cell deficiency. In addition, the long-term outcomes of both sepsis (PICS) and COVID (long COVID) share multiple neurocognitive and immune abnormalities. Sepsis endotypes may predict severity in the COVID group, which also indicates similarities in the pathophysiology of the two diseases [79, 80].

Differences that existed in both groups regarding antiviral responses and heme metabolism upon admission to the ICU and disappeared after a week suggest that the two diseases have the same pathophysiological processes typical of severe sepsis and that severe COVID should be treated like sepsis, particularly in the later disease stages. On the contrary, given that an early antiviral response distinguishes patients with severe COVID sepsis from those with non-COVID sepsis, immunomodulatory drugs developed to treat COVID could be repurposed and tested in patients with sepsis because sepsis currently has no specific treatment other than antibiotics and maintenance therapy. For example, tocilizumab, a monoclonal antibody against the IL-6 receptor [81], and baricitinib (not registered in the State Register of Medicines), a monoclonal antibody against the signaling protein kinases JAK1 and JAK2, activated in response to IL-6 signaling [82], have demonstrated clinical efficiency in COVID.

ENDOTYPES OF SEPSIS. SEVERE FORMS OF COVID — VIRAL SEPSIS

The heterogeneity of septic syndrome, individual clinical variability, and lack of prognostic and predictive markers hinder accurate early diagnosis, identification of patients with high-risk, and initiation of appropriate therapy. This greatly affects early and late clinical presentation, complications, and mortality, whereas unnecessary use of antibiotics is associated with the emergence of resistance. These findings have led to the reconceptualization of sepsis as a syndrome consisting of several endotypes that correspond to different biologically based and clinically relevant groups of patients with varying degrees of severity and clinical outcomes. Endotypes explain well the heterogeneous nature of sepsis syndrome, in contrast to earlier paradigms that consider sepsis as a single disease. Patients who were seriously ill or died tended to be distributed across all endotypes. Because sepsis is defined by a dysfunctional response to infection, patients with a reprogrammed or suppressed immune system typically experience higher clinical severity of the disease and increased mortality [83].

Blood transcriptomics is useful in characterizing immune responses that are disrupted in sepsis. Gene expression analysis of whole blood from patients with presumed sepsis from the Netherlands, Colombia, Canada, and Australia predicted five stable sepsis endotypes with specific but overlapping pathogenetic mechanisms. Based on the quantitative assessment of small gene expression signatures in the whole blood, a prognostic model has been developed that identifies sepsis endotypes regardless of the disease stage, origin, and location of infection, and accurately predicts the disease course, organ dysfunction, and mortality. Patients with early sepsis, even before a formal diagnosis, can be classified into neutrophil-suppressive (NPS), inflammatory (INF), innate immune (IHD), IFN, and adaptive (ADA) endotypes. The gene expression signature used for

endotype classification showed excellent results (AUC, 0.96; sensitivity, 81%; specificity, 95%). The NPS endotype distinguishes the most severely immunosuppressed patients with the poorest prognosis [83]. T.E. Sweeney et al. [84] obtained similar results by applying a classifier of three sepsis endotypes (inflammatory, adaptive and coagulopathic) to patients with COVID. The IFN endotype is characterized by the activation of multiple inflammatory pathways. These endotypes are associated with high subsequent SOFA scores and prolonged hospital stay, and sepsis-induced neutrophil dysfunction is associated with more severe symptoms, increased risk of hospital-acquired and secondary infections, and mortality [83].

Clinically, gene expression signatures identified in patients admitted in the ICU may be less useful because the patients' conditions have already deteriorated and they require intensive care and antibiotics. However, immune signatures can be used to triage and treat patients with an early sepsis. The determination of markers of disease severity and/or endotype within the first hours after hospitalization in addition to currently used criteria (such as SOFA score, cytokine levels, lactate, CRP, and assessment of systemic noninfectious inflammation) will allow for timely aggressive and/or immunomodulatory interventions for preventing progression to septic shock while sparing broad-spectrum antibiotics when they are not required. For example, immunosuppression associated with the NPS endotype suggests the early use of immune reconstitution therapy (IFN- γ , granulocyte-macrophage colony-stimulating factor, and IL-7) [85]. The inflammatory profile of the IFN endotype defines a group of patients who may benefit from targeted anti-inflammatory therapy. IFN, IHD, and ADA endotypes with a more favorable prognosis require monitoring without immediate antibiotic therapy [83].

Patients with severe COVID may presents with disease manifestations typical of sepsis, including ARDS and multiple organ failure. Signs of sepsis, such as immunosuppression, organ damage (such as lungs and kidneys), and long-term depression, are common in patients with severe COVID. Viral [86] and bacterial [87] sepsis cases were diagnosed in at least 50% of patients with severe COVID. A. Baghela et al. [88] suggested that diagnostic tools used in the treatment of sepsis of any origin, such as clinical indicators, biomarkers, and gene expression signatures, should be extended to patients with COVID, and they analyzed the transcriptome of "early" (1–5 days after hospitalization) and "late" (6–20 days after hospitalization) whole blood samples taken from such patients. Their results showed that early and late sample signatures were significantly different ($p < 0.0001$ for all comparisons) when comparing severe-to-moderate conditions, particularly in late samples, indicating a strong degree of dysregulation. Because of the small size of these predictive signatures (8–12 genes), they can be translated into clinical practice. Patients with COVID belong to the same endotypes as patients with sepsis. This means

that the mechanisms determining the COVID course are similar to those detected in sepsis and may be represented by the specific gene expression signatures that characterize this syndrome. Gene expression signatures corresponding to cellular reprogramming (8 genes), organ dysfunction (12 genes), and lethality (10 genes) are highly accurate in predicting severe sepsis and organ dysfunction. These same signatures predict disease severity and mortality in patients with COVID. The expression of septic gene signatures in patients with severe COVID indicates that these patients should be classified as having severe sepsis and that these signatures should be considered in diagnostics and treatment using repurposed drugs (repurposing is a new use of a drug with established safety records and clinical efficiency evidence for treatment for other indications). Clinical criteria [SOFA and multiple organ dysfunction score (MODS)], biomarkers, and immunomodulatory therapies proposed for the treatment of sepsis can probably be used for COVID.

Several mechanisms disrupted in COVID have been involved in the pathogenesis of sepsis, including those that control neutrophil activity, inflammatory cytokine secretion, and adaptive immune system response, supporting the notion that severe COVID is a subset of sepsis. Genetic signatures of sepsis, particularly those reflecting cellular reprogramming organ dysfunction, and mortality, are mediators of COVID pathogenesis and distinguish groups of patients with varying degrees of COVID severity. The signature of monocyte reprogramming to a tolerant phenotype is closely associated with the severity of viral infections, including COVID, and the signature of lethality indicates 30-day mortality quite well, indicating that similar mechanisms are functioning in severe COVID and severe sepsis of any origin. Correlating differential gene expression with clinical status showed that the expression of thousands of genes is disrupted in severe COVID. The differential expression patterns of heme metabolism and the need for respiratory support in patients with COVID with severe and moderate disease, those who survived, and those who died in hospital overlap with similar patterns in patients with sepsis. Genes with increased expression are involved in neutrophil degranulation, inflammation, interferon (IFN- α , IFN- β , and IFN- γ) and anti-inflammatory (IL-4 and IL-13) signaling, oxidative stress, coagulation, and complement functioning. Downregulated genes control adaptive immune pathways, programmed cell death, and TCR signaling. This means that T-cell responses are suppressed in severe COVID, which corresponds to severe sepsis of any origin. The activity and/or abundance of immature neutrophils and suppression of heme metabolism, most pronounced in deceased patients, are characteristic signs of severe COVID sepsis, as well as sepsis of any origin progressing to organ dysfunction.

The discovery of sepsis endotypes in patients with COVID supports the view that severe COVID represents viral sepsis and that sepsis endotypes may be useful for clinical risk

stratification in COVID. This implies that severe COVID can be predicted using the same biomarkers and gene expression signatures used in patients with sepsis of any etiology and that patients with COVID sepsis may be treated using targeted immunomodulatory therapies that correct dysfunctional immune processes characteristic of a certain endotype. This is relevant given the fact that antiviral therapy does not show significant efficiency in reducing mortality in patients with COVID [89].

Thus, COVID endotyping may provide prognostic criteria and a precision approach to characterize (and potentially treat) the disease. In the future, the clinical management of patients with COVID will be based on existing prognostic tools and those under development relevant to sepsis signatures and therapeutic options that focus on immune response dysregulation [88].

ADDITIONAL RISK FACTORS

Monocyte distribution width (MDW), a parameter proposed as a diagnostic test for severe infection and measured in new generation hematology analyzers, is the standard deviation of the mean cell volume of monocytes. COVID and sepsis increase MDW values. The pool of blood monocytes is very dynamic and consists of subpopulations of classical (CD14⁺CD16⁻ phenotype), intermediate (CD14⁺CD16⁺), nonclassical (CD14^{lo}CD16⁺), and double-negative (CD14^{lo}CD16^{lo}) cells. Comparison of monocyte volumetric parameters in sepsis and COVID using flow cytometry revealed differences in cell volume variability between COVID and sepsis [91]. In both pathologies, the proportion of classical monocytes decreased to a greater extent in sepsis than in COVID (median proportion, 59% in sepsis, 72% in COVID, and 80% in healthy controls). In septic samples, a relative decrease in the count of classical monocytes was accompanied by an increase in the proportion of intermediate and nonclassical cells, whereas in COVID, the frequency of the double-negative CD14^{lo}CD16^{lo} population increased. The variability in the volume of double-negative cells is significantly less in COVID than in sepsis and healthy controls. An increase in MDW was associated with a decrease in the frequency of classical monocytes and an increase in the proportion of intermediate monocytes. In COVID, the size range of monocytes (from smallest to largest) decreased, whereas in sepsis, it increased. In the process of studying correlations between changes in MDW and changes in other phenotypic markers, differential expression of the monocyte activation marker CD169 (type I IFN-inducible receptor [90]) was discovered, whose activity is increased in COVID (particularly in intermediate and nonclassical monocytes) and suppressed in sepsis [91].

The MDW is a new hematological parameter indicating the cytomorphological changes in monocytes that occur after activation. A. Malinowska et al. [92] summarized the available data on MDW as a diagnostic marker of infection and revealed that it can be used as a reliable marker for sepsis and

respiratory viral infections, including SARS-CoV-2. The most important advantage of MDW for infectious disease screening is its routine availability. The combined diagnostic accuracy of MDW for sepsis and COVID is similar to or superior to that of other sepsis biomarkers, including procalcitonin and CRP. At present, not a single biomarker has been identified with a combination of high diagnostic efficiency and routine availability. However, this parameter should be interpreted in the context of all available clinical and laboratory data.

EFFICIENCY OF HEMOSORPTION IN COVID AND SEPSIS

A retrospective study [93] compared the laboratory and clinical results of cytokine hemosorption as an immunomodulatory therapy in patients with COVID in the ICU with or without sepsis. The levels of procalcitonin, CRP, and ferritin were determined as indicators of infection/sepsis, and the levels of the cytokines IL-6, IL-8, IL-10, and TNF- α were determined as indicators of cytokine storm. The therapy was successful in reducing cytokine concentrations, and the results of all measurements after hemosorption did not differ between patients with and without sepsis. After hemosorption, all indicators decreased, except for the concentration of procalcitonin in patients with COVID sepsis. It was significantly higher in these patients than in patients without sepsis, whereas ferritin concentration and mortality showed no significant difference between the two groups. This suggests that hemosorption of cytokines is safe for treating patients with critical COVID. Thus, the progression of sepsis in patients with COVID can be avoided using cytokine hemosorption as an immunomodulatory therapy [93].

A comparative retrospective analysis of the survival of patients on venovenous ECMO with COVID-associated ARDS and severe ARDS of other pulmonary etiologies showed [94] that irreversible respiratory failure was the leading cause of death in the COVID group, whereas uncontrolled sepsis and multiple organ failure were the leading causes in other patient groups. Patients with ARDS associated with influenza and ARDS of other etiologies more often died from uncontrolled sepsis and multiple organ failure (mortality rates, 46% and 63%, respectively) compared with the COVID group (35%). The COVID ARDS group had lower SOFA and APACHE II scores at the initiation of ECMO (8 and 16, respectively, and lower). Concentrations of CRP (177 mg/L in COVID ARDS vs 222 mg/L in influenza and 271 mg/L for ARDS of other etiologies) and procalcitonin (0.3 μ g/L for COVID ARDS vs 10.3 μ g/L for influenza and 2.6 μ g/L for ARDS of other etiologies) in the COVID group were increased less significantly than in other groups. In ICU patients discharged from the hospital, no difference in 180-day survival was found between the groups [94].

Bleeding and thrombosis are common complications of ECMO in the COVID group. A relationship has been established

between the inflammatory status, coagulation, bleeding, and thrombosis in patients receiving venovenous ECMO for respiratory failure in COVID. The mean LDH level in ECMO nonsurvivors (47%) was significantly increased compared with survivors (1046 vs 489 U/L). Platelet/fibrinogen dysfunction, as evidenced by low peak amplitude on blood viscoelasticity testing, was more pronounced in survivors (65 vs 75 mm). Nonsurvivors had a significantly reduced platelet count during the first 7 days of ECMO (140 vs 189.5 cells/ μ L), and higher concentrations of D-dimer were also noted (21 vs 14 μ g/mL) compared with survivors. In ECMO nonsurvivors, a strong correlation was found between clinical markers of inflammation and coagulation markers, with higher rates of bleeding (73% vs. 35%), digital ischemia (47% vs. 12%), ARF (60% vs. 12%), and sepsis (60% vs. 23.5%). The correlation between inflammation and coagulation in ECMO nonsurvivors indicates a dysregulated inflammatory response and predicts poorer clinical outcomes [95].

CONCLUSION

According to the findings of many researchers, severe COVID forms meet the criteria of the third international consensus "Sepsis-3." In its most severe form, COVID bears striking similarities to sepsis, a life-threatening organ dysfunction caused by a dysregulated immune response to infection. These two conditions have many parallels at the clinical, pathogenetic, and molecular level, whereas the identified differences and contradictions relate mainly to the quantitative values of clinical, diagnostic, and prognostic indicators. Bacteria are the predominant causative agent of sepsis, whereas sepsis caused by viruses has been underestimated. SARS-CoV-2 has again attracted the attention of doctors and researchers to viral sepsis. Many published papers refer to patients with "sepsis caused by the SARS-CoV-2." Most authors who have conducted retrospective or prospective comparative analyses of COVID and sepsis refer to severe COVID as a typical septic viral infection. However, COVID-associated sepsis has some characteristics that need to be considered when making therapeutic decisions.

ADDITIONAL INFORMATION

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