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Laboratory abnormalities associated with COVID-19

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Introduction

Coronavirus disease 2019 (COVID-19), a form of respiratory and systemic zoonosis caused by a virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), belonging to the *Coronaviridae* family. It has been highlighted that laboratory medicine plays an essential role in the early detection, diagnosis and management of COVID-19. With patients now being admitted with COVID-19, laboratory medicine also plays an important role in assessing disease severity, prognostication and therapeutic monitoring. The aim of this article is to provide a brief overview on the most frequent laboratory abnormalities encountered in patients with COVID-19 infection.

Virus particles spread through the respiratory mucosa, initially using the angiotensin converting enzyme 2 (ACE-2) receptor at ciliated bronchial epithelial cells, and then infect other cells. This induces a cytokine storm in the body and generates a series of immune responses, that cause changes in peripheral white blood cells and immune cells such as lymphocytes.

With regards to complications and death, a third of patients presented with acute respiratory distress syndrome (ARDS), but also, albeit in a lower frequency, acute cardiac injury, acute kidney injury, and shock, eventually followed by multiple organ failure. Therefore, early identification and timely treatment of critical cases is of crucial importance.[1]

Pathophysiology: Immune dysregulation

Damage to lymphocytes, including T lymphocytes by SARS-CoV-2 leads to lymphopaenia, predisposing to secondary bacterial infections and exacerbating severity. An increase in levels of pro-inflammatory cytokines, and decrease in anti-inflammatory cytokines may indicate T cell mediated response against SARS-CoV-2 resulting in a cytokine storm that causes hyperinflammation. Upregulation of pro-inflammatory cytokines in serum was found associated with severe pulmonary damage and inflammation.

Pathophysiology: Kidney Injury

ACE-2 serves as a receptor for SARS-CoV-2. SARS-CoV-2 can bind to renal epithelial cells, injure these cells, and subsequently disrupt whole body fluid, acid-base, and electrolyte homeostasis.[2] Postmortem evaluations demonstrated severe acute tubular injury, prominent lymphocyte infiltration, detection of viral antigen in tubular epithelial cells, macrophage infiltration, and complement C5b-9 deposition. The lymphocyte and immune cell infiltration found in COVID-19-induced acute kidney injury (AKI) is likely an important pathophysiologic factor.[3] The associated high mortality from AKI may be due to deleterious lung-kidney crosstalk during COVID-19 infection and augmentation of inflammation during AKI.[4]

Pathophysiology: Liver Injury

Available data supports a higher prevalence of abnormal aminotransferase levels in severe COVID-19, but clinically significant liver injury is uncommon. Elevation in liver enzymes may be from hepatic damage from immune interactions involving intrahepatic cytotoxic T cells and Kupffer cells. Drug-induced liver injury may also be a possible contributing factor to the observed abnormal liver function.[5]

Table 1. Laboratory abnormalities noted in patients with COVID-19

Laboratory Abnormalities	Potential Clinical Significance
Increased white cell count	2-fold increase in patients requiring ICU admission[6]
Increased neutrophil count	4.4-fold increase in patients requiring ICU admission[6]
Decreased lymphocyte count	0.4-fold, i.e. decreased in patients requiring ICU admission[6]
Decreased platelets	Indication of consumption (disseminated) coagulopathy
Increased ESR	
Increased D-dimer	Activation of blood coagulation and/or disseminated coagulopathy – 4.8-fold increase in patients requiring ICU admission[6]
Increased CRP	Viral infection/sepsis
Increased PCT	Bacterial (super)infection
Increased IL-6	Cytokine storm
Increased ferritin	Cytokine storm
Increased lactate dehydrogenase (LDH)	Pulmonary injury and/or widespread organ damage
Increased cardiac troponin	Cardiac injury
Increased NT pro-BNP	Cardiac injury
Increased creatinine	Renal injury
Increased aminotransferases (ALT/AST)	Liver injury and/or widespread organ damage
Decreased albumin	Impairment of liver function

Prognostication and predicting ICU admission

Early identification and timely treatment of critical cases is of crucial importance.[7] Several significant differences were noted between patients who needed admission to the intensive care unit (ICU) and those who did not. In a study published by Huang and colleagues involving 140 COVID-19 patients (13 with severe disease), some significant predictors of ICU admission were leukocytosis (2.0-fold increased in ICU patients), neutrophilia (4.4-fold increased), lymphopaenia (0.4-fold, i.e. decreased), D-dimer (4.8-fold increased), ALT (1.8-fold increased), LDH (1.4-fold increased) and procalcitonin, whose values were increased in 25% of patients who were admitted to the ICU compared with 0% who were not ($p = 0.029$).[6] Fan et al found that admission lymphopaenia and increased LDH stood out as discriminating laboratory indices with a P value of < 0.001 and 0.005, respectively. They also noted a down trending LDH as patients' clinical condition improved.[8] In a study published by Zhou et al the median time from illness onset to invasive mechanical ventilation was 14.5 days (12.0 – 19.0).[9]

Predicting mortality

In the study by Wang et al white blood cell counts, neutrophil counts and D-dimer were higher in non-survivors than those in survivors. As disease progressed and clinical status deteriorated, the levels of serum urea and creatinine progressively increased before death.[10] Tang and colleagues followed 183 patients with confirmed COVID-19 infection during their hospital stay, and found that coagulation parameters were more frequently deranged in those who died ($n = 21$) than in those who survived – 71% of patients who died fulfilled the criteria for diagnosing disseminated intravascular coagulation (DIC) compared to only 0.6% of those who survived.[11]

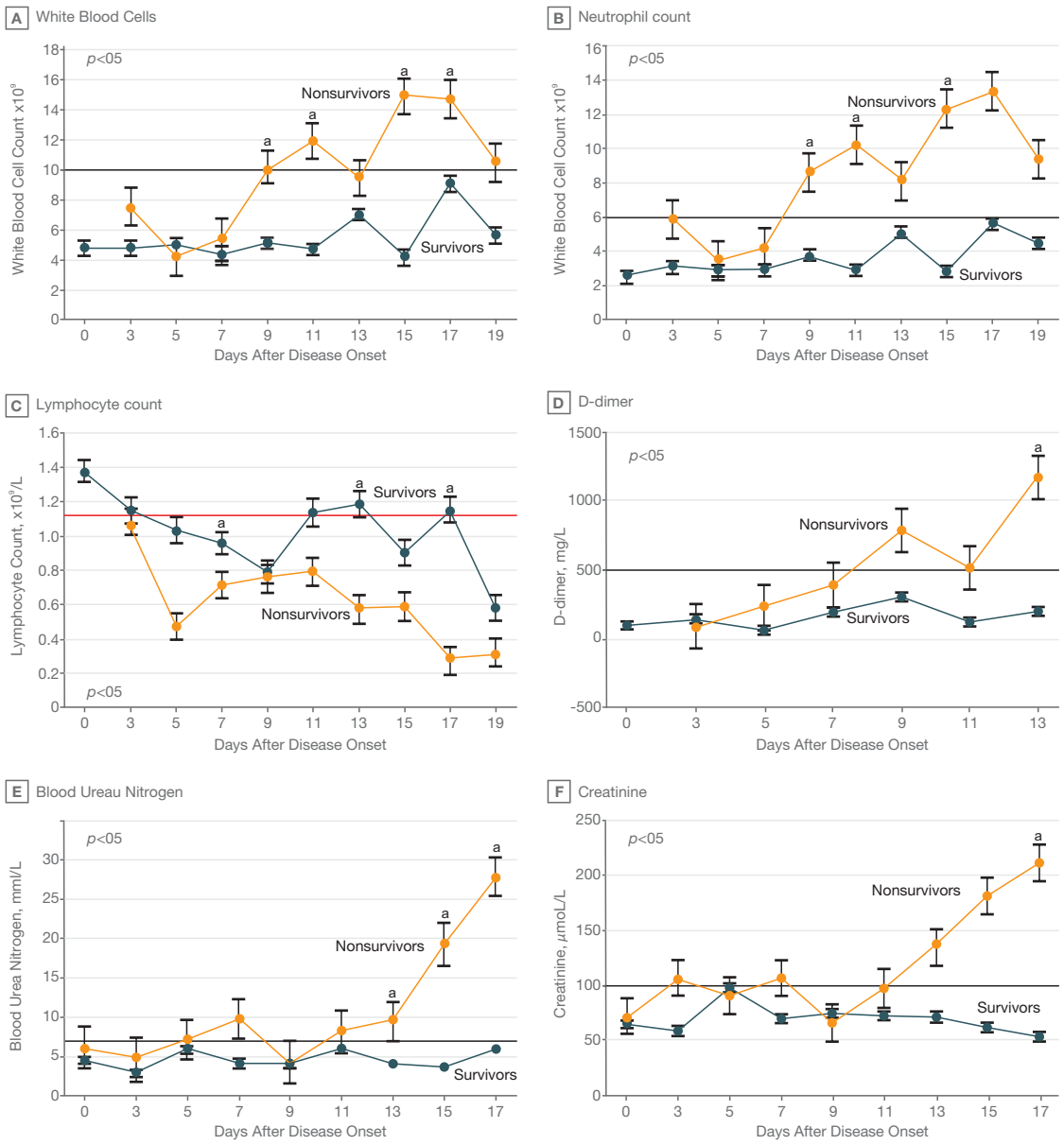

Figure 1. Laboratory parameters in 33 patients with COVID-19 (Reference 10)

D-dimer

Endothelial damage and subsequent clotting is common in severe and critical patients with COVID-19. In one study, patients with a D-dimer level over 1 μg/L at admission had increased mortality.[9]

Procalcitonin

Procalcitonin (PCT) typically remains within the reference range in patients with uncomplicated SARS-CoV-2 infection,[12] and PCT does not appear substantially altered in patients with COVID-19 at admission. The progressive increase of its value seemingly mirrors a worse prognosis. This is not unexpected, whereby serum procalcitonin levels are typically normal in patients with viral infections (or viral sepsis), whilst its gradual increase probably mirrors bacterial superinfection.[13] Serial procalcitonin measurement may play a role in predicting evolution towards a more severe form of disease.[12]

Lactate dehydrogenase

Lactate dehydrogenase (LDH) is an enzyme present in essentially all major organs. It has previously been shown that elevated LDH may indicate lung damage.[14]

Neutrophilia and lymphopaenia

Neutrophilia may be related to cytokine storm induced by virus invasion.[10] Lymphocytes in most patients with COVID-19 are reduced.[7,15] This suggests that COVID-19 mainly acts on lymphocytes, especially T lymphocytes, as does the related virus SARS-CoV. Damage to T lymphocytes might be an important factor leading to exacerbation of disease.[9] In a study by Qin and colleagues, an increased neutrophil-to-lymphocyte ratio (NLR) was found in the severe group of patients with COVID-19 compared to the mild group.[16] An increased NLR has been shown to be an early indicator of severe illness.[17] Patients with age $\geqslant$ 50 years and NLR $\geqslant$ 3.13 progressed to severe illness, and they should rapidly access intensive care units if necessary.

IL-6

Higher serum levels of pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) and chemokines (IL-8) are found in patients with severe COVID-19 compared to individuals with mild disease, similar to the results seen during the SARS and MERS outbreaks.[16] Serum COVID-19 viral load (RNAaemia) is strongly associated with cytokine storm. Chen et al found inflammatory cytokine IL-6 levels to be significantly elevated in critically ill patients, with values almost 10-fold higher in critically ill patients. More importantly, the extremely high IL-6 level was closely correlated with COVID-19 viral load (R = 0.902).

Secondary haemophagocytic lymphohistiocytosis is a hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multi-organ failure. As during previous pandemics associated with coronaviruses (Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome), corticosteroids are not routinely recommended and might exacerbate COVID-19-associated lung injury. However, in hyperinflammation, immunosuppression may be beneficial.[18]

Lancet Laboratories offers testing for IL-6, which is performed on an SST sample.

Conclusion

The care of patients with COVID-19 entails early identification, rapid isolation, timely establishment of infection prevention and control measures, together with symptomatic care for patients with mild disease and supportive treatment for those with severe COVID-19. Laboratory tests play an important role in the diagnosis, risk stratification, prognosis and therapeutic monitoring of patients with COVID-19.

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