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EDITORIAL

Laboratory biomarkers and prognosis in Covid-19, where do we stand?

Coronavirus Disease 2019 (Covid-19) has a wide range of clinical manifestations. Studies have estimated that while 30%–60% of Covid-19 cases are asymptomatic, up to 5% of symptomatic cases are critically ill, characterised by respiratory compromise and multiorgan failure.[1-3] Therefore, early detection and timely treatment of critical patients, or those likely to progress to a critical condition, is paramount for clinicians. Despite our understanding of the clinicopathological features of Covid-19 growing at pace with the rapid release of data, the correlation of changes in laboratory parameters to the prognosis of patients remains ever changing.[2] Several systematic reviews and meta-analyses have identified increased levels of white blood cells (WBC), lymphopenia (especially CD8+ cells), thrombocytopaenia, increased lactate-dehydrogenase (LDH), creatine kinase (CK), C-reactive protein (CRP), D-dimer and levels of pro-inflammatory cytokines (such as IL-6) to be associated with more severe inflammatory responses and consequent lung damages, with a greater need for intensive care unit (ICU) support and increased mortality rates.[2-5] However, a greater knowledge of the prognostic biomarkers for patients with Covid-19 could enhance the timing of interventions, and the better allocation of resources, since hospital and ICU capacity is stretched across healthcare systems during this pandemic.[2,4]

The systematic review and meta-analysis by Le Huu Nhat Minh and colleagues collated clinical information from 62,909 confirmed cases of Covid-19 across 148 studies; with an aim to identify the laboratory factors associated with Covid-19, and how they relate to the severity of infection.[6] Their findings mirror what has been observed in the wider literature. Increased levels of inflammatory markers (CRP, D-dimer and LDH) and WBC (mainly neutrophils) with decreasing numbers of lymphocytes and platelets were associated with increasing severity of Covid-19 infection; along with signs of end-organ dysfunction; such as deranged liver enzymes and impaired kidney function.[2,4,6,7]

Although the authors should be commended for their work, there are still many questions left unanswered due to limitations in their study design. According to World Health Organisation official figures, by the end of the week of their search (16/03/2020), only 159,926 cases of Covid-19 had been formally identified.[8] Therefore, it difficult to draw substantial conclusions from the studies they analysed, as they originate from a time when knowledge of the disease was still in its infancy and standardised diagnostic workups had yet to be formalised.[2,4] Similarly, the biomarkers assessed during that timeframe did not fully reflect what is now known about the clinical features of Covid-19. For example, through 2020, it became evident that a major cause of mortality and morbidity from Covid-19 was associated with the increased risk of thromboembolic events, primarily pulmonary embolism, deep vein thrombosis, peripheral artery thrombosis and acute ischaemic stroke.[2,4,9] An analysis of the risk of thromboembolism and subsequent prognosis would have added greatly to their findings.

Further to this, their category of 'survivor' for Covid-19 severity is inherently vague and somewhat limited. It does not inform the reader of the level of care the patient received (such as mechanical ventilation vs. continuous positive airway pressure), and more importantly does not account for the now recognised long-term sequelae associated with Covid-19.[3] Their analysis would be greatly enhanced by the inclusion of the correlation of clinical biomarkers and features of so called 'long Covid syndrome', such as impaired lung function, fatigue, muscle weakness, and anxiety and depression.[3] Finally, a large percentage of Covid-19 cases are asymptomatic, and it is now understood that they present with similar laboratory findings as do symptomatic cases[1]; therefore, for completeness, an analysis of asymptomatic patients incorporated into their scale of severity would have enhanced their findings.

Specific blood biomarkers associated with increased disease severity include reduced lymphocytes as they are the key to maintain adequate immune responses.[4] Specifically, to Covid-19, it has been hypothesised that lymphocytes express SARS-CoV-2 receptor ACE2, and hence are attacked and depleted by fellow lymphocytes.[4] Raised proinflammatory cytokines in severe Covid-19 illness, including TNF-a and IL-6, are likely to result in lymphocyte-induced apoptosis, posing an additional mechanism for depleted lymphocyte levels.[4] There is evidence to suggest that increased levels of pro-inflammatory mediators, including CRP, CK and LDH, are associated with increased disease severity.[4] CRP is a non-specific acute phase protein, produced via IL-6 in the liver, and hence is associated with increased inflammation and more severe infection.[4,5,10] Raised CK is reflective of muscular damage, which is likely to be due to antigen-antibody deposition in muscle, and increased circulating viral toxins.[11] One study found an approximate fourfold increase in CK in patients who had a more severe disease course of Covid-19.[4] Additionally, rhabdomyolysis has been reported as a possible late complication of Covid-19 infection.[12]

A study by Cai et al. showed that 76.3% of Covid-19 patients had abnormal liver tests, and that this increases the likelihood of developing severe pneumonia.[13] SARS-CoV and MERS-CoV, which are biologically similar to SARS-CoV-2, are associated with viral infiltration of hepatocytes, and increase in mitotic cells and eosinophil infiltration, leading to liver cell apoptosis.[7] It is thought that SARS-CoV-2 may also induce liver injury via a similar mechanism.[7]

Elevated D-dimer has been shown to be associated with poorer outcomes.[4,9] The inflammatory response that is associated with Covid-19 infection, and hypoxia secondary to pneumonia, ultimately results in a hypercoagulable state.[4,9] One study showed that D-dimer levels could effectively predict in-patient mortality of Covid-19 patients.[4,9] There is evidence that anticoagulation therapy, with low molecular weight heparin or unfractionated heparin, is therapeutic in cases involving coagulopathy.[12]

Neutrophil to lymphocyte ratio (NLR) could also be a valuable future tool in determining prognosis of patients with Covid-19. Patients with more advanced Covid-19 disease have been found to have significantly higher NLR than at earlier stages of infection.[14,15] Interestingly, NLR has been found to have greater diagnostic accuracy than CURB-65 and MuLBSTA scoring assessment tools.[16] However, without defined cut-off values, NLR can be difficult to interpret and is reliant on clinician experience.

There is evidence to suggest that raised serum glutamic oxaloacetic transaminase, sodium and potassium are significant predictors of disease severity.[17] These novel biomarkers could be of use in identifying severe disease early, and hence halting disease early in its course.

Covid-19 has had a profound global impact, highlighting a need to for continual development and research into biomarkers which determine disease severity. The aforementioned laboratory biomarkers are key to effective management and monitoring of patients with Covid-19, and additionally enable effective risk stratification of patients with Covid-19.

KEYWORDS

biomarkers, coronavirus, Covid-19, pathology

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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