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Perspective

Mild versus severe COVID-19: Laboratory markers

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ABSTRACT

The number of COVID-19 patients is dramatically increasing worldwide. Treatment in intensive care units (ICU) has become a major challenge; therefore, early recognition of severe forms is absolutely essential for timely triaging of patients. While the clinical status, in particular peripheral oxygen saturation (SpO2) levels, and concurrent comorbidities of COVID-19 patients largely determine the need for their admittance to ICUs, several laboratory parameters may facilitate the assessment of disease severity. Clinicians should consider low lymphocyte count as well as the serum levels of CRP, D-dimers, ferritin, cardiac troponin and IL-6, which may be used in risk stratification to predict severe and fatal COVID-19 in hospitalised patients. It is more likely that the course of the disease will be unfavourable if some or all of these parameters are altered.

As the number of COVID-19 patients is dramatically increasing worldwide and treatment in intensive care units (ICU) has become a major challenge, early recognition of severe forms of COVID-19 is absolutely essential for timely triaging of patients. SARS-CoV-2 infection, especially in older patients and those with pre-existing illness, can progress to severe disease with critical respiratory symptoms and significant pulmonary changes visible by imaging techniques. The changes include ground glass opacities, patchy consolidation, alveolar exudates and interlobular involvement, ultimately prognosticating deterioration (Huang et al., 2020). Further to the recognised risk factors such as old age and underlying comorbidities–particularly cardiovascular diseases, diabetes, respiratory diseases, and other conditions (Zhou et al., 2020)–several markers have been identified that modulate the course of COVID-19. This paper summarises the laboratory markers that might be useful in indicating progression from mild to severe disease (Table 1).

COVID-19 patients admitted to ICUs have been found to have higher concentrations of proinflammatory cytokines and, importantly, increased secretion of those T-helper-2 (Th2) cytokines suppressing inflammation (Huang et al., 2020). Given the high levels of cytokines induced by SARS-CoV-2, treatment to reduce inflammation-related lung damage is critical. However, any intervention to reduce inflammation will negatively affect viral clearance. Among the various inflammatory cytokine and chemokine levels assessed in several studies, tumour necrosis factor alpha (TNF-α), interferon-γ-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), chemokine (C-C motif), ligand 3 (CCL-3), and distinct interleukins (IL) (IL-2, IL-6, IL-7, IL-10) were significantly associated with disease severity and particularly observed among cases admitted to ICUs. IL-1 and IL-8 were not associated with severity (Table 1). Apparently, the serum levels of some interleukins have the potential to discriminate between mild and severe disease and possibly may be used as prognostic markers.

Among haematological parameters, lymphopenia is clearly associated with disease severity; patients who have died from COVID-19 have had significantly lower lymphocyte counts than survivors. In fact, repletion of lymphocytes may be an important factor for recovery (Henry, 2020). Other blood cells–including white blood cells, neutrophils, eosinophils, platelets, and CD8 cell counts–were partial predictors in discriminating mild from severe COVID-19 (Table 1); their significance is still ambiguous. Granulocyte colony stimulating factor (G-CSF) has been found to be elevated in ICU patients and significantly associated with disease severity (Table 1).

Patients with severe COVID-19 appear to have more frequent signs of liver dysfunction than those with milder disease. An increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin levels has been observed among

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Table 1
Haematological, cytokine, liver enzyme and coagulation parameters in mild versus severe COVID19 patients.

Haematological parameters	COVID-19 cases (n)	Interpretation	Reference
White blood cell count (WBC)	15 mild, 9 severe, 5 critical cases	normal or ↓ in 23/29	(Chen et al., 2020a)
	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
	43 (28 mild, 15 severe)	normal in all cases	(Gao et al., 2020)
	1,994 cases (meta-analysis)	↓ in 29% of cases	(Li et al., 2020a)
	54 cases	normal in cases	(Li et al., 2020b)
Neutrophil count	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
	201 cases	↑ in ARDS cases	(Wu et al., 2020)
	12 cases	↓ in most cases	(Liu et al., 2020a)
Lymphocyte count	Familial cluster, 6 cases	↓in 2 of 3 cases > 60 years	(Chan et al., 2020)
	15 mild, 9 severe, 5 critical cases	↓ in 20/29	(Chen et al., 2020a)
	41 cases (13 ICU cases)	↓ in ICU cases	(Huang et al., 2020)
	140 cases	↓ in most cases	(Zhang et al., 2020b)
	43 (28 mild, 15 severe)	normal in cases	(Gao et al., 2020)
	1,994 cases (meta-analysis)	↓ in most cases	(Li et al., 2020a)
	54 cases	↓ in most cases	(Li et al., 2020b)
	12 cases	↓ in most cases	(Liu et al., 2020a)
	30 cases	↓ in 40% cases	(Liu et al., 2020b)
	70 mild, 85 severe cases	↓ in all cases	(Mo et al., 2020)
Eosinophil count	140 cases	↓ in most cases	(Zhang et al., 2020b)
Thrombocyte count	Familial cluster, 6 cases	↓ in 2 of 3 cases > 60 years	(Chan et al., 2020)
	70 mild, 85 severe cases	normal; slightly lower in severe cases	(Mo et al., 2020)
Granulocyte-colony stimulating factor (G-CSF)	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
CD8 cell count	12 cases	↓ in most cases	(Liu et al., 2020a)

Cytokines	COVID-19 cases (n)	Interpretation	Reference
Tumour necrosis factor alpha (TNF-alpha)	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
Interferon-γ induced protein 10 (IP-10)	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
Monocyte chemoattractant protein 1 (MCP-1)	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
Chemokine (C-C Motif) Ligand 3 (CCL-3)	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
Interleukin-1 (IL-1)	15 mild, 9 severe, 5 critical cases	normal in all cases	(Chen et al., 2020a)
Interleukin-2 (IL-2)	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
Interleukin-2 receptor (IL-2R)	15 mild, 9 severe, 5 critical cases	↑, > critical > severe > mild	(Chen et al., 2020a)
Interleukin-6 (IL-6)	15 mild, 9 severe, 5 critical cases	↑ according to severity > critical > severe > mild	(Chen et al., 2020a)
	69 cases, mortality 7.5%	↑ in the patient group with $SpO_2 < 90\%$	(Wang et al., 2020b)
	150 cases	↑ in non-survivors	(Mehta et al., 2020)
	43: 28 mild, 15 severe cases	↑ in severe cases	(Gao et al., 2020)
	70 mild, 85 severe cases	↑; higher in severe cases	(Mo et al., 2020)
Interleukin-7 (IL-7)	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
Interleukin-8 (IL-8)	15 mild, 9 severe, 5 critical cases	normal in all cases	(Chen et al., 2020a)
Interleukin-10 (IL-10)	15 mild, 9 severe, 5 critical cases	normal in all cases	(Chen et al., 2020a)
	69 cases, mortality 7.5%	↑ in the patient group with $SpO_2 < 90\%$	(Wang et al., 2020b)
	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)

Liver enzymes/biomarkers	COVID-19 cases (n)	Interpretation	Reference
Albumin	15 mild, 9 severe, 5 critical cases	↓in 15/29	(Chen et al., 2020a)
	41 cases (13 ICU cases)	↓ in ICU cases	(Huang et al., 2020)
	12 cases	↓ in most cases	(Liu et al., 2020a)
	70 mild, 85 severe cases	↓ in all cases	(Mo et al., 2020)
Alanine aminotransferase (ALT)	15 mild, 9 severe, 5 critical cases	-	(Chen et al., 2020a)
	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
Aspartate aminotransferase (AST)	15 mild, 9 severe, 5 critical cases	-	(Chen et al., 2020a)
Total bilirubin	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
	15 mild, 9 severe, 5 critical cases	- normal in all cases	(Chen et al., 2020a)
Glucose	43: 28 mild, 15 severe cases	↑ in severe cases	(Gao et al., 2020)
Serum creatinine	126 mild, 24 severe cases	↑ in severe cases	(Chen et al., 2020a)
Lactate dehydrogenase (LDH)	Familial cluster, 6 cases	↑ in the 3 cases >60 yrs.	(Chan et al., 2020)
	15 mild, 9 severe, 5 critical cases	↑ in 20/29	(Chen et al., 2020a)
	69 cases, mortality 7,5%	↑ in the patient group with $SpO_2 < 90\%$	(Wang et al., 2020b)
	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
	201 cases	↑ in ARDS cases	(Wu et al., 2020)
	1,994 cases (meta-analysis)	↑ in 28% of cases	(Li et al., 2020a)
	54 cases	↑ in most cases	(Li et al., 2020b)
	12 cases	↑ in all cases	(Liu et al., 2020a)
	70 mild, 85 severe cases	↑ in severe cases	(Mo et al., 2020)
C-reactive protein (CRP)	Familial cluster, 6 cases	↑ in the 3 cases >60 yrs.	(Chan et al., 2020)
	126 mild, 24 severe cases	higher in severe cases	(Chen et al., 2020b)
	15 mild, 9 severe, 5 critical cases	↑ in 27/29	(Chen et al., 2020a)
	69 cases, mortality 7,5%	↑ in cases with $SpO_2 < 90\%$	(Wang et al., 2020b)
	140 cases	↑ in severe cases	(Zhang et al., 2020b)
	43: 28 mild, 15 severe cases	↑ in severe cases	(Gao et al., 2020)
	1,994 cases (meta-analysis)	↑ in 44% of cases	(Li et al., 2020a)
	54 cases	↑ in most cases	(Li et al., 2020b)
	12 cases	↑ in most cases	(Liu et al., 2020a)
	70 mild, 85 severe cases	↑ in all cases, higher in severe cases	(Mo et al., 2020)
Procalcitonin (PCT)	140 cases	↑ in severe cases	(Zhang et al., 2020b)

Table 1 (*Continued*)

Liver enzymes/biomarkers	COVID-19 cases (n)	Interpretation	Reference
	70 mild, 85 severe cases	↑ in all cases	(Mo et al., 2020)
Ferritin	150	↑ in non-survivors	(Mehta et al., 2020)
NT-proBNP	126 mild, 24 severe cases	↑ in severe cases	(Chen et al., 2020b)
Cardiac troponin I	126 mild, 24 severe cases	↑ in severe cases	(Chen et al., 2020b)
Cardiac troponin I (meta-analysis)	218 mild, 123 severe cases	↑ in severe cases	(Lippi et al., 2020)
	138 hospitalised severe cases	↑ in severe cases	(Wang et al., 2020a)
Angiotensin II level	12 cases	↑ in cases	(Liu et al., 2020a)

Coagulation parameters	COVID-19 cases(n)	Interpretation	Reference
d-dimers	191 cases, 91 with comorbidities	↑ in non-survivors	(Zhou et al., 2020)
	94 cases	↑ in cases vs. controls	(Han et al., 2020)
	201 cases	↑ in ARDS cases	(Wu et al., 2020)
	140 cases	↑ in severe cases	(Zhang et al., 2020b)
	43: 28 mild, 15 severe cases	↑ in severe cases	(Gao et al., 2020)
	30 cases	↑ in 17% of cases	(Liu et al., 2020b)
	70 mild, 85 severe cases	normal; slightly higher in severe cases	(Mo et al., 2020)
	183 cases; 21 non-survivors	↑ in all cases, higher in non-survivors	(Tang et al., 2020)
Antithrombin (AT)	94 cases	↓ in cases vs. controls	(Han et al., 2020)
Prothrombin time (PT)	94 cases	↓ in cases vs. controls	(Han et al., 2020)
	41 cases (13 ICU cases)	↑ in ICU cases	(Huang et al., 2020)
	183 cases; 21 non-survivors	↑ in non-survivors	(Tang et al., 2020)
Activated partial thromboplastin time (APTT)	183 cases; 21 non-survivors	↑ in non-survivors	(Tang et al., 2020)
Thrombin clotting time (TCT)	94 cases	shorter in critical cases vs. controls	(Han et al., 2020)
	43: 28 mild, 15 severe cases	↑ in severe cases	(Gao et al., 2020)
Fibrin degradation products (FDP)	94 cases	↑ in cases vs. controls	(Han et al., 2020)
	183 cases; 21 non-survivors	↑ in non-survivors	(Tang et al., 2020)
Fibrinogen	94 cases	↑ in cases vs. controls	(Han et al., 2020)
	43: 28 mild, 15 severe cases	↑ in severe cases	(Gao et al., 2020)
	183 cases; 21 non-survivors	↑ in all cases, higher in non-survivors	(Tang et al., 2020)

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; CD8, cluster of differentiation 8; SpO_2, Peripheral oxygen saturation; NT-proBNP, N-terminal pro b-type natriuretic peptide

many ICU patients (Zhang et al., 2020a) (Table 1). Infection of liver cells with SARS-CoV-2 cannot be excluded as 2–10% of patients with COVID-19 have diarrhoea and viral RNA has been detected in both stool and blood samples, which implies the possibility of hepatic virus presence (Yeo et al., 2020). It is also likely that any immune-mediated inflammation, in particular cytokine storm, but also pneumonia-associated hypoxia, may lead to liver damage in critically ill COVID-19 patients (Zhang et al., 2020a). C-reactive protein (CRP) levels are increased in COVID-19 patients and it has been shown that survivors had median CRP values of approximately 40 mg/L, while non-survivors had median values of 125 mg/L, indicating a strong correlation with disease severity and prognosis (Ruan et al., 2020) (Table 1). Other predictors of poor outcome include the serum levels of ferritin and lactate dehydrogenase (LDH). Elevated ferritin levels due to secondary haemophagocytic lymphohistiocytosis (sHLH) and cytokine storm syndrome have been reported in severe COVID-19 patients. Based on body temperature, organomegaly, blood cell cytopenia, triglycerides, fibrinogen, AST and ferritin levels, a predictive H-score has been proposed to estimate the risk of developing secondary haemophagocytic lymphohistiocytosis (Mehta et al., 2020).

Correlations of abnormal coagulation parameters with poor prognosis have been observed (Table 1). Non-survivors have shown significantly higher levels of plasma D-dimers and fibrin degradation products, increased prothrombin times and activated partial thromboplastin times compared to survivors (Tang et al., 2020). Coagulopathy and overt disseminated intravascular coagulation appear to be associated with high mortality rates. Among the coagulation parameters, D-dimer elevation > 1 ug/L was the strongest independent predictor of mortality (Zhou et al., 2020). Elevated cardiac troponin I levels indicating heart injury were also predictive of mortality in critically ill patients (Lippi et al., 2020; Wang et al., 2020a).

The haematological and coagulation parameters summarised here and increased inflammatory reactions caused by various cytokines and liver enzymes are a globally observed phenomenon in COVID-19 patients. While the clinical status (in particular SpO_2 levels) and concurrent comorbidities of COVID-19 patients largely determine the need for their admittance to ICUs, several laboratory parameters may facilitate the assessment of disease severity and rational triaging. It is more likely that the course of the disease will be unfavourable if some or all of these parameters are altered. Clinicians should consider low lymphocyte count and the serum levels of CRP, D-dimers, ferritin, cardiac troponin and IL-6, which may be used in risk stratification to predict severe and fatal COVID-19 in hospitalised patients. In order to further support clinical decision-making, large datasets and sound meta-analyses are now urgently required.

Conflict of interest

All authors disclose no conflict of interest.

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