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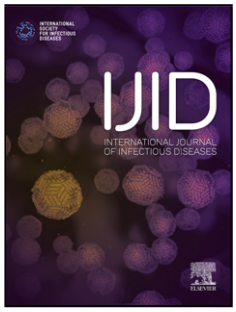

Mild versus severe COVID-19: laboratory markers

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Mild versus severe COVID-19: laboratory markers

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Abstract:

The number of COVID-19 patients is increasing dramatically worldwide and treatment in intensive care units (ICU) has become a major challenge, the early recognition of severe forms of 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 determines the need of their admittance to ICUs, several laboratory parameters may facilitate the assessment of disease severity. In hospitalized patients, clinicians should consider low lymphocyte count as well as the serum levels of CRP, D-dimers, ferritin and IL-6 which may be used in risk stratification to predict severe and fatal COVID-19. The more several or all of these parameters are altered, the more likely it is that the course of the disease will be unfavourable.

Highlights

- several laboratory parameters may facilitate the assessment of COVID-19 severity
- discriminating mild from severe COVID-19 disease.
- Cumulative data from clinical characteristics of COVID-19 patients
- low lymphocyte count as well as the serum levels of CRP, D-dimers, ferritin and IL-6.

As the number of COVID-19 patients is increasing dramatically worldwide and treatment in intensive care units (ICU) has become a major challenge, the 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, 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 [1]. Further to recognized risk factors such as old age and underlying comorbidities, in particular cardiovascular diseases, diabetes, respiratory diseases and other conditions [2], several markers have been identified that modulate the course of COVID-19. Here we summarize laboratory markers that might be useful in indicating progression from mild to severe disease (Table 1).

COVID-19 patients admitted to ICUs had higher concentrations of proinflammatory cytokines and, importantly, increased secretion of those T-helper-2 (Th2) cytokines suppressing inflammation [1]. Given the high levels of cytokines induced by SARS-CoV-2, treatment to reduce inflammation-related lung damage is critical. Any intervention to reduce inflammation will, however, affect negatively the 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 (Table1). Apparently, the

serum levels of some interleukins bear 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 died from COVID-19 had significantly lower lymphocyte counts than survivors. In fact, repletion of lymphocytes may be an important factor for recovery [3]. Other blood cells, including white blood cells, neutrophils, eosinophils, platelets and CD8 cell counts were partly only predictors in discriminating mild from severe COVID-19 (Table1); their significance is still ambiguous. Granulocyte colony stimulating factor (G-CSF) was elevated in ICU patients and significantly associated with the severity of disease (Table1).

Patients with severe COVID-19 appear to have signs of liver dysfunction more frequently than those with milder disease. An increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin levels has been observed among many ICU patients [4] (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 [5]. 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 [4]. 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 [6] (Table 1). Other predictors of poor outcome include the serum levels of ferritin and lactate dehydrogenase (LDH). Elevated ferritin levels due to secondary hemophagocytic lymphohistiocytosis (sHLH) and cytokine storm syndrome have been reported in severe COVID-19 patients. Based on body temperature, organomegaly, blood cell cytopenia, triglycerides, fibrinogen as well as AST and ferritin levels, a predictive H-score was proposed to estimate the risk of developing secondary hemophagocytic lymphohistiocytosis [7].

Correlations of abnormal coagulation parameters with poor prognosis were observed (Table 1). Non-survivors showed significantly higher levels of plasma D-dimers and fibrin degradation products, increased prothrombin times and activated partial thromboplastin times compared to survivors [8]. 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 [2]. Elevated cardiac troponin I levels indicating heart injury are also predictive of mortality in critically ill patients [9;10].

The haematological and coagulation parameters summarized here as well as 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 determines the need of their admittance to ICUs, several laboratory parameters may facilitate the assessment of disease severity and rational triaging. The more several or all of these parameters are altered, the more likely it is that the course of the disease will be unfavourable. In hospitalized patients, clinicians should consider low lymphocyte count as well as the serum levels of CRP, D-dimers, ferritin and IL-6 which may be used in risk stratification to predict severe and fatal COVID-19. In order to further support clinical decision making, large datasets and sound metanalyses are now urgently required.

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145 **Table 1: Haematological, Cytokines, Liver enzymes and Coagulation parameters in mild vs. severe COVID19 patients**
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Haematological parameters	COVID-19 cases/cases (n)	Interpretation	Reference
White blood cell count (WBC)	15 mild, 9 severe, 5 critical cases	normal or ↓ in 23/29	[11]
	41 cases (13 ICU cases)	↑ in ICU cases	[1]
	43 (28 mild, 15 severe)	normal in all cases	[13]
	1994 cases (meta-analysis)	↓ in 29% of cases	[15]
	54 cases	normal in cases	[16]
Neutrophil count	41 cases (13 ICU cases)	↑ in ICU cases	[1]
	201 cases	↑ in ARDS cases	[17]
	12 cases	↓ in most cases	[18]
Lymphocyte count	Familial cluster, 6 cases	↓in 2 of 3 cases >60 years	[19]
	15 mild, 9 severe, 5 critical cases	↓ in 20/29	[11]
	41 cases (13 ICU cases)	↓ in ICU cases	[1]
	140 cases	↓ in most cases	[20]
	43; 28 mild, 15 severe cases	normal in cases	[13]
	1994cases (meta-analysis)	↓ in most cases	[15]
	54 cases	↓ in most cases	[16]
	12 cases	↓ in most cases	[18]
	30 cases	↓ in 40% cases	[21]
	70 mild, 85 severe cases	↓ in all cases	[14]
Eosinophil count	140 cases	↓ in most cases	[20]
Thrombocyte count	Familial cluster, 6 cases	↓ in 2 of 3 cases >60 yrs.	[19]
	70 mild, 85 severe cases	normal; slightly lower in severe cases	[14]
Granulocyte-colony stimulating factor (G-CSF)	41 cases (13 ICU cases)	↑ in ICU cases	[1]
CD8 cell count	12 cases	↓ in most cases	[18]

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Cytokines	COVID-19 cases (n)	Interpretation	Reference

Tumour necrosis factor alpha (TNF-alpha)	41 cases (13 ICU cases)	↑ in ICU cases	[1]
Interferon-γ induced protein 10 (IP-10),	41 cases (13 ICU cases)	↑ in ICU cases	[1]
Monocyte chemoattractant protein 1 (MCP-1)	41 cases (13 ICU cases)	↑ in ICU cases	[1]
Chemokine (C-C Motif) Ligand 3 (CCL-3)	41 cases (13 ICU cases)	↑ in ICU cases	[1]
Interleukin-1 (IL-1)	15 mild, 9 severe, 5 critical cases	normal in all cases	[11]
Interleukin-2 (IL-2)	41 cases (13 ICU cases)	↑ in ICU cases	[1]
Interleukin-2 receptor (IL-2R)	15 mild, 9 severe, 5 critical cases	↑, >critical >severe >mild	[11]
Interleukin-6 (IL-6)	15 mild, 9 severe, 5 critical cases	↑ according to severity >critical >severe >mild	[11]
	69 cases, mortality 7,5%	↑ in the patient group with SpO_2<90%	[12]
	150 cases	↑ in non-survivors	[7]
	43; 28 mild, 15 severe cases	↑ in severe cases	[13]
	70 mild, 85 severe cases	↑; higher in severe cases	[14]
Interleukin-7 (IL-7)	41 cases (13 ICU cases)	↑ in ICU cases	[1]
Interleukin-8 (IL-8)	15 mild, 9 severe, 5 critical cases	normal in all cases	[11]
Interleukin-10 (IL-10)	15 mild, 9 severe, 5 critical cases	normal in all cases	[11]
	69 cases, mortality 7,5%	↑ in the patient group with SpO_2<90%	[12]
	41 cases (13 ICU cases)	↑ in ICU cases	[1]

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Liver enyzmes/biomarkers	**COVID-19 cases/cases (n)**	**Interpretation**	**Reference**
Albumin	15 mild, 9 severe, 5 critical cases	↓in 15/29	[11]
	41 cases (13 ICU cases)	↓ in ICU cases	[1]
	12 cases	↓ in most cases	[18]
	70 mild, 85 severe cases	↓ in all cases	[14]
Alanine aminotransferase (ALT)	15 mild, 9 severe, 5 critical cases	-	[11]
	41 cases (13 ICU cases)	↑ in ICU cases	[1]
Aspartate aminotransferase (AST)	15 mild, 9 severe, 5 critical cases	-	[11]
Total bilirubin	41 cases (13 ICU cases)	↑ in ICU cases	[1]
	15 mild, 9 severe, 5 critical cases	- normal in all cases	[11]
Glucose	43; 28 mild, 15 severe cases	↑ in severe cases	[13]
Serum creatinine	126 mild, 24 severe cases	↑ in severe cases	[11]

Lactate dehydrogenase (LDH)	Familial cluster, 6 cases	↑ in the 3 cases >60 yrs.	[19]
	15 mild, 9 severe, 5 critical cases	↑ in 20/29	[11]
	69 cases, mortality 7,5%	↑ in the patient group with SpO_2<90%	[12]
	41 cases (13 ICU cases)	↑ in ICU cases	[1]
	201 cases	↑ in ARDS cases	[17]
	1994 cases (meta-analysis)	↑ in 28% of cases	[15]
	54 cases	↑ in most cases	[16]
	12 cases	↑ in all cases	[18]
	70 mild, 85 severe cases	↑ in severe cases	[14]
C-reactive protein (CRP)	Familial cluster, 6 cases	↑ in the 3 cases >60 yrs.	[19]
	126 mild, 24 severe cases	higher in severe cases	[22]
	15 mild, 9 severe, 5 critical cases	↑ in 27/29	[11]
	69 cases, mortality 7,5%	↑ in cases with SpO_2<90%	[12]
	140 cases	↑ in severe cases	[20]
	43; 28 mild, 15 severe cases	↑ in severe cases	[13]
	1994 cases (meta-analysis)	↑ in 44% of cases	[15]
	54 cases	↑ in most cases	[16]
	12 cases	↑ in most cases	[18]
	70 mild, 85 severe cases	↑ in all cases, higher in severe cases	[14]
Procalcitonin (PCT)	140 cases	↑ in severe cases	[20]
	70 mild, 85 severe cases	↑ in all cases	[14]
Ferritin	150	↑ in non-survivors	[7]
NT-proBNP	126 mild, 24 severe cases	↑ in severe cases	[22]
Cardiac troponin I	126 mild, 24 severe cases	↑ in severe cases	[22]
Cardiac troponin I (meta-analysis)	218 mild, 123 severe cases	↑ in severe cases	[9]
	138 hospitalized severe cases	↑ in severe cases	[10]
Angiotensin II level	12 cases	↑ in cases	[18]

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Coagulation parameters	**COVID-19 cases/cases (n)**	**Interpretation**	**Reference**
d-dimers	191 cases, 91 with comorbidities	↑ in non-survivors	[2]

	94 cases	↑ in cases vs. controls	[23]
	201 cases	↑ in ARDS cases	[17]
	140 cases	↑ in severe cases	[20]
	43; 28 mild, 15 severe cases	↑ in severe cases	[13]
	30 cases	↑ in 17% of cases	[21]
	70 mild, 85 severe cases	normal; slightly higher in severe cases	[14]
	183 cases; 21 non-survivors	↑ in all cases, higher in non-survivors	[8]
Antithrombin (AT)	94 cases	↓ in cases vs. controls	[23]
Prothrombin time (PT)	94 cases	↓ in cases vs. controls	[23]
	41 cases (13 ICU cases)	↑ in ICU cases	[1]
	183 cases; 21 non-survivors	↑ in non-survivors	[8]
Activated partial thromboplastin time (APTT)	183 cases; 21 non-survivors	↑ in non-survivors	[8]
Thrombin clotting time (TCT)	94 cases	shorter in critical cases vs. controls	[23]
	43; 28 mild, 15 severe cases	↑ in severe cases	[13]
Fibrin degradation products (FDP)	94 cases	↑ in cases vs. controls	[23]
	183 cases; 21 non-survivors	↑ in non-survivors	[8]
Fibrinogen	94 cases	↑ in cases vs. controls	[23]
	43; 28 mild, 15 severe cases	↑ in severe cases	[13]
	183 cases; 21 non-survivors	↑ in all cases, higher in non-survivors	[8]

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

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