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AMPATH LAB UPDATE

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Role of inflammatory marker testing in COVID-19

Accumulating evidence suggests that inflammatory responses play a critical role in the progression of COVID-19.

The inflammatory response is triggered by rapid viral replication of SARS-CoV-2 and cellular destruction, leading to the recruitment of macrophages and monocytes and the induction and release of cytokines. These cytokines attract more immune cells and further activate the immune response, leading to a "cytokine storm".

Several inflammatory markers have been shown to be useful for detecting disease severity and fatality. Inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be significantly associated with high risks of the development of severe COVID-19[1].

Measurement of inflammatory markers might assist clinicians to monitor and evaluate the severity and prognosis of COVID-19[1].

Interleukin 6

Interleukin-6 and its role as a cytokine

Interleukin-6 (IL-6) acts locally and systemically, and on both lymphoid and non-lymphoid cells. Its actions include host defence (against *Candida* and *Listeria spp*), and growth and differentiation of B- and T-cells (including immunoglobulin production). It is also important for T-helper 17 cell differentiation and thus cytotoxic T-cell responses to viruses. IL-6 is a significant inducer of fever, inflammation and acute-phase proteins (e.g. CRP)[2]. IL-6 levels in serum are low in the absence of inflammation, but quickly rise when there are bacterial or viral infections, inflammation or trauma.

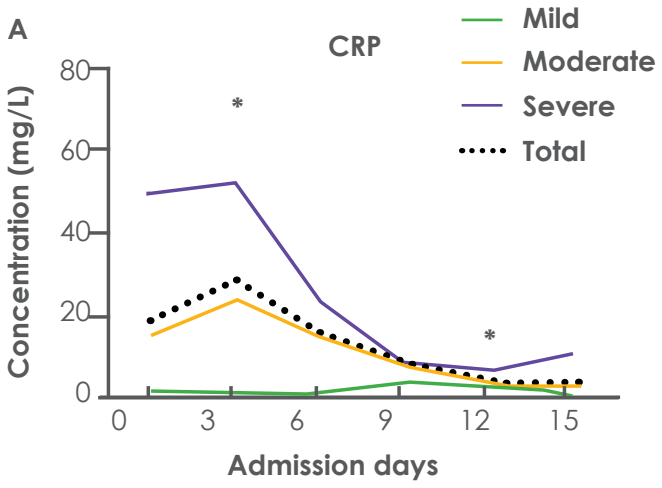
Findings in COVID-19 patients with regards to IL-6

There is evidence that a sub-group of COVID-19 patients present with severe disease that ultimately progresses to respiratory failure due to acute respiratory distress syndrome (ARDS). This is the leading cause of mortality and is due to the rapid onset of a hyperinflammatory syndrome due to hypercytokinaemia, resulting in multi-organ failure and death.

Suggested screening parameters for hypercytokinaemia or "cytokine storm" include unremitting fever, cytopaenias, increased ferritin and IL-6[3].

Predictors of mortality from a study in Wuhan, China, included elevated ferritin and an elevated IL-6. It was also shown that IL-6 levels may be used as a biomarker to evaluate severity[3].

This was confirmed in another study where IL-6 levels were significantly higher in patients with severe disease as compared to patients with moderate disease, and that the IL-6 levels correlated with RNAaemia (virus circulating in the blood). Patients who had detectable SARS-CoV-2 in their blood/serum had an IL-6 value greater than 100 pg/ml[4]. Furthermore, a decline in serum lactate dehydrogenase (LDH) or creatine kinase (CK) may predict a favourable response to the treatment of COVID-19, and also correlated with SARS-CoV-2 mRNA clearance from the blood[5].



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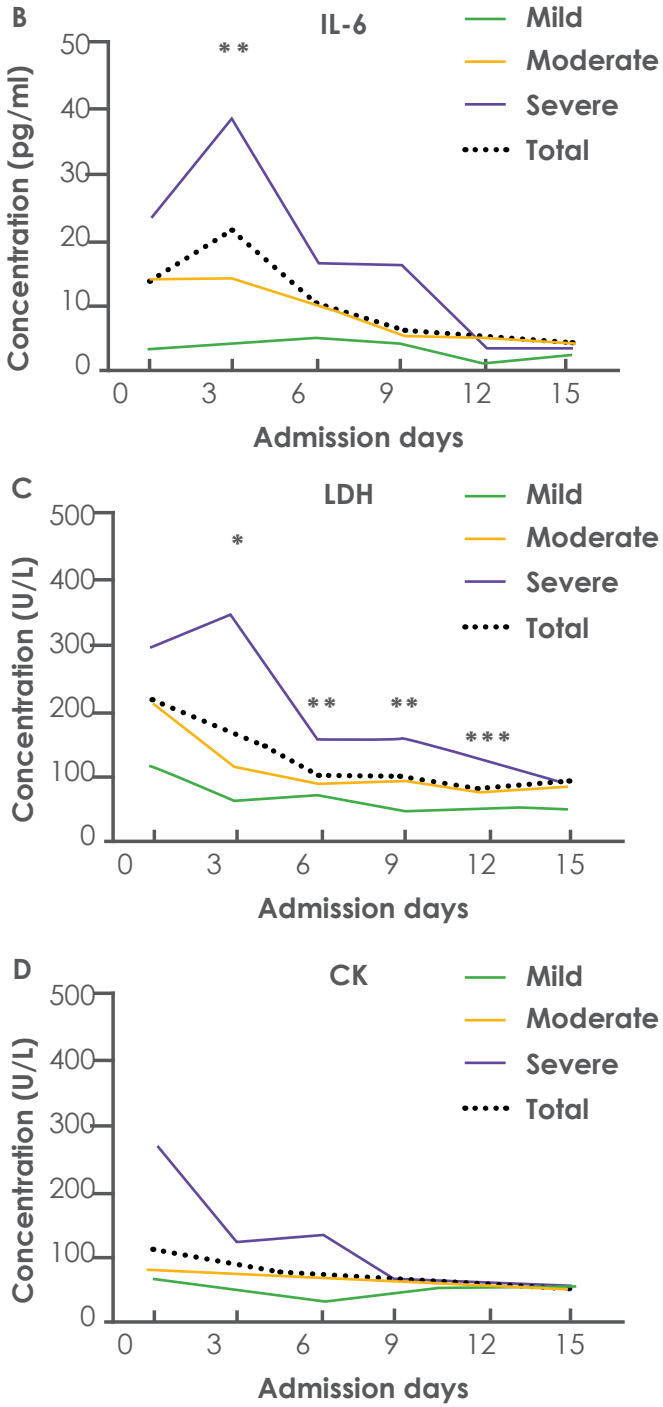

Figure1: Dynamic profile of blood biochemical factors[5]
***P <0.05 ** P<0.01 ***P<0.001**

Procalcitonin

Procalcitonin (PCT) is a well-known biomarker for bacterial infection. A recent meta-analysis of the literature suggests that serial PCT measurement may play a role in predicting evolution towards a more severe form of COVID-19 disease.

The production and release into the circulation of PCT from extrathyroidal sources is amplified during bacterial infections, actively sustained by enhanced concentrations of interleukin-1β, tumour necrosis factor-α and IL-6. Synthesis of this biomarker is inhibited by interferon-γ, whose concentration increases during viral infections. PCT values would therefore remain within the reference range in patients with non-complicated SARS-CoV-2 infection, whereby its substantial increase would reflect bacterial co-infection. A meta-analysis based on four studies showed that increased PCT values are associated with a nearly five-fold higher risk of severe SARS CoV-2 infection (pooled odds ratio 4.76; 95% CI, 2.74–8.29)[6].

- **PCT testing on admission** seems to be valuable for early risk assessment and to rule out bacterial co-infection in COVID-19 patients.
- **Monitoring of PCT** will be useful for the detection of secondary infections, progression to a more severe disease state, and to guide the initiation and cessation of antibiotics.

CRP

CRP is a sensitive but non-specific systemic marker of acute-phase response in inflammation, infection and tissue damage. A meta-analysis of several studies found that the mean level of CRP was higher in the severe group than the non-severe group of COVID-19 patients, although the difference was not always statistically significant. Most studies reported that CRP level was positively related to the severity of COVID-19[1].

Using univariate analysis, Wang et al calculated an odds ratio of 1.049 (95% CI, 1.028-1.070; P <.001) when CRP is used to predict the progression from mild to severe disease. On multivariate regression the odds ratio was 1.056 (95% CI, 1.025-1.089; P <.001). Patients with severe disease had higher levels of CRP (median, 43.8 vs 12.1 mg/L; P <.001)[7].

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