Q&A Slides

HyTest Webinar - Biomarkers of Inflammation: Interleukin-6 and Beyond

1. **What tests are used for prognosis in patients with COVID-19?**

Leukocyte parameters
According to International Federation of Clinical Chemistry (IFCC) guidelines complete blood count is recommended in patients with SARS-CoV-2 infection (Thompson et al., 2020). It has been demonstrated that lymphopenia is present in almost all symptomatic patients. There is evidence that the magnitude of lymphocyte count reduction associates with disease severity.

An elevated neutrophil count has been found to predict poor prognosis. Therefore, an elevated neutrophil-to-lymphocyte ratio can be used as a marker of adverse outcomes.

Coagulation tests
According to interim guidance published by International Society of Thrombosis and Haemostasis, for hospitalized patients with SARS-CoV-2 infection it is recommended to monitor D-dimer, prothrombin time, platelet count, and fibrinogen for determining prognosis (Thachil J et al., 2020). An elevated D-dimer has been associated with unfavorable disease progression. The low platelet count is another aspect that characterizes unfavorable disease progression.

Inflammatory markers
Increased CRP concentration has been shown to be associated with poor outcome. Erythrocyte sedimentation rate (ESR) is an inflammatory marker which may be considered as an alternative to CRP. Higher erythrocyte sedimentation rate is associated with adverse outcomes in SARS-CoV-2 infection.

Procalcitonin may be helpful in identifying patients with bacterial co-infections who have a worse prognosis.

Serum ferritin is elevated in most patients. High ferritin concentration is associated with adverse outcome.

Cardiovascular biomarkers
Cardiac involvement may frequently develop in patients with SARS-CoV-2 infection. It has been shown that cardiac troponins are higher in patients with more severe illness, compared to those with milder disease. There is strong association between elevated troponin and adverse outcomes in these patients.

Biomarkers of multisystem organ failure
SARS-CoV-2 infection can be associated with liver injury. Elevated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin, low albumin and prealbumin concentrations have all been associated with poor outcome.

Kidney injury is a relatively frequent complication in patients with COVID-19, especially in those with severe illness. Elevations of both serum creatinine and blood urea nitrogen (BUN) have been associated with unfavorable clinical outcome.

Lactate dehydrogenase (LDH) is a non-specific marker of tissue damage. Elevated lactate dehydrogenase was associated with adverse outcome.

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2. What are the requirements for IL-6 immunoassays?

There are several clinical features of IL-6 defining technical requirements for IL-6 immunoassays. First, normal values of IL-6 are about 1-710 pg/ml. In hyper-inflammatory state IL-6 levels could be as high as 10000 pg/ml. All that defines the need for assay to have high sensitivity and wide linearity range. Besides, assay needs to have low cross-reactivity with other cytokines which levels in the blood comparable to IL6 and can compromise measurements.

3. What is the most clinically utilized biomarker for prognosis and monitoring of treatment in patients with COVID-19 disease?

Currently there is no evidence that a single biomarker can be used for prognosis and monitoring of treatment in patients with COVID-19.

For example, the DISCOVER study recruited 187 patients with COVID-19 admitted to a UK hospital and analyzed a panel of biomarkers including interleukin-6, soluble urokinase plasminogen activator receptor suPAR, Krebs von den Lungen 6, troponin, ferritin, lactate dehydrogenase, BNP, and procalcitonin on the admission blood sample (Arnold et al., 2021). The goal of the study was to identify whether any individual biomarker had prognostic significance for the poor outcome. It was concluded that admission blood biomarkers have only moderate predictive value for predicting COVID-19 outcomes. IL-6 and suPAR had the best performance.

In a study from Germany involving 89 patients who were hospitalized with COVID-19, it has been demonstrated that IL-6 and CRP were highly predictive of respiratory failure (Herold et al., 2021). For each patient, the admission level and maximum level of each parameter was assessed. Maximal IL-6 level predicted respiratory failure with the highest accuracy. Therefore, it was concluded that IL-6 and CRP are useful markers that predict respiratory failure with high accuracy. Elevated IL-6 levels in the course of disease predicted respiratory failure significantly earlier than CRP did.

In a study from New York City including 5279 patients with COVID-19 it has been demonstrated that increased troponin, CRP and D-dimer were strongly associated with critical illness (Petrilli et al., 2020).

In another study from New York City including 2782 hospitalized COVID-19 patients CRP and D-dimer levels at the time of initial presentation were each independently associated with adverse events (Smilowitz et al., 2021). Patients were at highest risk when they presented with concomitant elevations in CRP and D-dimer concentrations. In addition, authors investigated the relationship between IL-6 and outcomes in a smaller group of patients who had CRP and IL-6 measured at hospital presentation. In this group, IL-6 was independently associated with adverse outcomes in patients with high and low initial CRP concentrations. These results suggest that IL-6 may provide additional prognostic information in patients hospitalized with COVID-19.

On the contrary, in a study from Europe including 639 critically ill patients with confirmed SARS-CoV-2 infection, IL-6 levels remained similar in intensive care unit survivors and non-survivors during the ICU stay (Garcia et al., 2020). Results of the study suggest that only creatinine, D-dimer, lactate, potassium, pulmonary function at admission and history of ischemic heart disease are predictors of mortality in critically ill patients with COVID-19.

In conclusion, multiply biomarkers in combination with clinical and demographic data are used for prognosis and monitoring of patients with SARS-CoV-2 infection. Larger validation studies are required to confirm clinical utility of candidate biomarkers.

4. **How does IVD manufactures in China consider the value of inflammation biomarkers? Is that different in US or Europe?**

According to the clinical guidelines of infectious and critical care medicine in China, IL-6 had been recommended as the early biomarker of acute infections. Now, in China, IL-6 is always combined with PCT together to serve on the treatment and diagnosis of infections or inflammation. CRP is used in Europe, China and Japan as an inflammation marker, whereas in US CRP is considered as a cardiac marker. The main market for serum amyloid A, according to the sales data, is China.

5. **Utility of serum amyloid A (SAA) measurements in patients with COVID-19.**

Serum Amyloid A (SAA) is an acute-phase protein mainly produced by the liver in response to proinflammatory cytokines. SAA concentration in blood increases in patients with COVID-19. In several studies, mostly from China, it has been demonstrated that SAA concentrations were significantly higher in patients with more severe disease, and in those who did not survive during follow-up when compared to patients with milder forms of the disease or those who survived during follow-up. The measurement of SAA, alone or in combination with other clinical and demographic parameters, might be useful for risk stratification and clinical monitoring in patients with COVID-19.

In a study involving 3265 patients hospitalized with COVID-19, SAA, CRP, high sensitivity CRP, IL-6, procalcitonon, and lymphocyte count were compared in their ability to predict risk of disease progression from mild to more advanced types of COVID-19 (Yu et al., 2020). In this study the predictive value of SAA level for the disease progression was higher compared to other inflammatory biomarkers. Moreover, the combination of SAA with procalcitonin and lymphocyte count was identified as the most sensitive parameter for the prediction of risk of disease progression.

However, there is not enough evidence that SAA add any clinical value beyond that already obtained through measurement of more standard inflammatory markers. Therefore, routine measurement of SAA in patients with COVID-19 cannot be recommended in the absence of further research on clinical utility.

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