INTRODUCTION

Acute respiratory distress syndrome (ARDS) is the most common cause for respiratory failure in critical patients, and also the main factor responsible for poor prognosis. Recently, there have been more and more refined diagnostic criteria for ARDS. In addition to clinical parameters, biomarkers have gradually received attention from researchers. This article presents some biomarkers that have been widely studied in recent years.

Clara cell secretory protein (CCSP, CC16)

Clara cells are non-ciliated epithelial cells mainly found in the epithelium of terminal bronchioles and respiratory bronchioles. With active proliferation and differentiation, Clara cells are involved in the repair process of bronchial epithelial injuries. CC16, the main product that Clara cells secrete, is composed of two identical peptide chains and has anti-inflammatory and anti-fibrotic biological properties.

In a prospective, multi-center observational study with 78 ARDS cases enrolled, serum CC16 levels, duration of mechanical ventilation, number of ventilator-free days, organ failure and cause of death were monitored while 28-day mortality rate was assessed. It found that the CC-16 levels were significantly higher in non-survivors than survivors on Days 0-2, and sustained up to Day 14. It also found that the CC-16 levels were correlated positively with the number of failing organs and length of mechanical ventilation. Thus, it concluded that higher initial CC-16 serum level was associated with increased risk of death, fewer ventilator-free days and increased frequency of non-pulmonary multiple organ failure and that CC-16 was a valuable biomarker of ARDS that may help predict outcome. Determann et al.[2] have conducted a retrospective research on the correlation between CC16 and acute lung injury and/or ARDS. In their research, 22 patients with ventilator-associated pneumonia (VAP) and 15 control patients were enrolled. Plasma CC16 had a good diagnostic capacity for acute lung injury (ALI)/ARDS when the receiver operating characteristic curve had an area under the curve of 0.91. Identification of ALI/ARDS patients by sudden increases in plasma CC16 of 30% or more yielded a sensitivity of 90% and a specificity of 92%. Moreover, levels of CC16 increased before the diagnosis of ALI/ARDS. Plasma CC16 thus seems a potential biological marker for ALI/ARDS. A recent study of 150 patients showed that the CC16 level began to increase...
4 days after ALI and/or ARDS was diagnosed and that the CC16 level was correlated with acute kidney injury (AKI) score, sequential organ failure assessment (SOFA) score and oxygenation index. For this reason, CC16 may serve as an indicator of lung injury in the Intensive Care Unit (ICU).\(^{[1]}\)

**Pulmonary surfactant-associated protein D (SP-D)**

SP is a surface-active lipoprotein complex formed by type II alveolar epithelial cells and Clara cells. Currently, four types of SPs have been found, namely SP-A, SP-B, SP-C and SP-D. Recently, SP-D, especially its relation to some diseases, has become a hot topic of research. Determann et al.\(^{[8]}\) observed 16 patients who were incubated and mechanically ventilated because of ALI/ARDS and 20 patients without lung injury at the onset of mechanical ventilation. Levels of biological markers were measured retrospectively at baseline and after 2 days of mechanical ventilation. Their findings showed that in ALI/ARDS patients, SP-D level increased over time and that it was related to mortality, duration of mechanic ventilation and length of hospital stay. However, they said that further research was needed to reveal the relationship between SP-D and some commonly used scores in the ICU. In the literature,\(^{[9]}\) SP-D level was also monitored. Similarly, SP-D level began to increase on the fourth day. Quite different from CC16, the SP-D level was not closely correlated with lung injury score, SOFA score and oxygenation index all the time, but only on the fourth day. However, researchers still hold that SP-D may serve as an early biomarker of ALI for patients on mechanic ventilation and offer no comments as to whether SP-D can be a biomarker to predict the ALI prognosis. SP-D may be an indicator for early diagnosis of ARDS. Fifty-five patients who developed ARDS following abdominal operations during 2010-2012 were collected. Their serum SP-D levels were measured on Days 0, 3, 5 and 7. The findings showed that SP-D levels were always higher in the ARDS group than in the non-ARDS group. It also concluded that SP-D ≤ 253.0 μg/L can be a sensitive and specific biomarker for the early diagnosis of ARDS.\(^{[9]}\)

From the above researches of various types seen, as with CC16, SP-D increases in the early stage of ALI and/or ARDS, and thus it is helpful in their early diagnosis. As it is correlated with mortality rate and length of hospital stays, SP-D levels may help to predict the prognosis to some degree. Now that research has been scarce in this regard, more prospective controlled studies are expected.

**Inflammatory cell activation markers**

**Interleukin-8 (IL-8)**

IL-8, an important neutrophil chemokine, has been proven to be correlated with disease severity as well as with prognosis. The serum IL-8 level is significantly higher in ARDS patients than in normal healthy controls, indicating that the serum IL-8 level can reveal lung injury and the severity of disease.\(^{[10]}\) Research also shows that IL-8 concentration in bronchoalveolar lavage fluid (BALF) is significantly increased in ARDS patients and that the IL-8 level is significantly higher in the pulmonary edema fluid of ARDS patients than that in pulmonary edema patients due to elevated hydrostatic pressure.\(^{[11]}\) Donnelly et al.\(^{[12]}\) have studied the relationship between IL-8 concentration in BALF and ARDS among the high-risk ARDS population. They put forward that increased IL-8 concentration in BALF may help to predict early ARDS in high-risk ARDS patients. Animal studies have found that pretreatment with IL-8 antibody in animals can significantly attenuate or even completely prevent acid aspiration or structural damage resulting from lipopolysaccharide (LPS)-induced pulmonary edema, with a markedly lower acute mortality rate. This research has further confirmed the role that IL-8 plays in the pathogenesis of ARDS induced by certain risk factors.\(^{[13]}\) A number of controlled studies have shown that the presence of infectious factors may contribute to IL-8 production. IL-8 concentration in pulmonary edema fluid is higher in sepsis-induced ARDS than in non-sepsis-induced ARDS. In addition, circulating IL-8 concentrations in patients with multiple organ failure of septic origin is also higher than those with non-septic origin.\(^{[14]}\) Previous studies have demonstrated that the initial part of the A allele in IL-8 synthesis has single nucleotide polymorphisms (IL-8-251A/T, rs4073). For this reason, Wacharasint et al.\(^{[15]}\) tested the hypotheses that there was a certain relationship between IL8-251A/T and ARDS. In their research, IL8-251A/T of the enrolled 1384 cases was classified. IL-8 mRNA was tested in vitro and then a rank test was conducted among the genotypes and the incidence of severe ARDS and mortality rate. The results showed that compared with the AT group or TT group, AA group had the highest incidence of severe ARDS. However, no statistically significant difference was observed in mortality rate. That is to say, the AA genotype in IL-8-251A/T may increase the incidence of ARDS. Currently, the diagnostic value of IL-8 for ARDS induced by different factors has not been fully determined, but it has a good predictive value for ARDS caused by infection and may also help to predict prognosis. However, with regard to its value for people of different age groups, researches are inadequate.

**Tumor necrosis factor-α (TNF-α)**

Studies have long shown that plasma TNF-α is significantly increased in patients with ALI and ARDS. It is a key cytokine leading to ALI and ARDS. Animal studies have shown that in a double-hit model of trauma-induced septic ALI, TNF receptor-1 contributes to apoptotic and inflammatory response.\(^{[16]}\) In a rat research, Li et al.\(^{[17]}\) have confirmed that TNF-α plays an initiating role in extracorporeal circulation-induced acute lung injury. Studies have shown that TNF-α, as a regulator of inflammatory cells and endothelial cells, is
able to regulate inflammation and promote tissue healing. In severe trauma, macrophages release large amounts of TNF-α into the blood circulation. It not only activates itself but also promotes the secretion of other cytokines (such as IL-10, IL-6, etc.). It also induces production of nitric oxide, endothelin, oxygen free radicals and other media, triggering the cascade effect and hence causing systemic inflammatory response syndrome (SIRS) and damage to the structure and function of organs. As a consequence, low blood pressure, ALI and/or ARDS, disseminated intravascular coagulation and ultimately multiple organ dysfunction syndrome (MODS) ensue. Some scholars, however, believe that TNF-α, as a regulator of inflammation, is not specific to lung tissues and thus not specific to the severity of lung tissue injuries. Currently, researches on TNF-α are mostly concerned with animal studies. More prospective clinical studies are needed to further clarify the role of TNF-α in the early diagnosis and prognosis of ALI/ARDS.

Matrix metalloproteinase-9 (MMP-9)

By comparing MMP-9 levels between healthy adults and ARDS patients, Toril et al.\(^\text{[15]}\) found that MMP-9 were significantly higher in ARDS patients than in healthy adults. Pugin et al.\(^\text{[16]}\) also found that the MMP-9 levels in the BALF of ARDS patients were significantly higher either than that of patients with cardiogenic pulmonary edema or that of normal control subjects. Some scholars have demonstrated that MMP-9 and MMP-2 levels in the BALF were positively correlated with increased arterial-alveolar gradient of oxygen tension in a swine model of cardiopulmonary bypass, which indicates that high concentrations of MMP-9 and MMP-2 are closely related to the development of ALI. Eichler et al.\(^\text{[17]}\) built a murine model of ALI expressing no MMP-9 and a corresponding wild-type murine model of ALI. The findings showed that the severity of lung injury was significant lesser in the former than in the latter.

Procalcitonin (PCT) and soluble receptors on myeloid cells triggers-1 (sTREM-1)

PCT cannot be detected in healthy people. It is elevated when inflammatory diseases and serious systemic infection are present, and sustains a low level when non-infectious factors are present (such as viral infection, trauma). PCT peaks in the early stage of severe bacterial infection and sustains up to 24 h. Currently, PCT is widely used in clinical practice as a biomarker of systemic inflammation, especially of bacterial infection, with a good correlation. Detection of PCT may help to differentiate in the early stage whether ARDS is induced by infectious diseases. Especially for ARDS caused by community pneumonia, PCT helps to assess the severity of disease and to reduce the blind use of antibiotics.\(^\text{[18-22]}\) A number of studies show that continuously elevated PCT is correlated with severe infection, multiple organ dysfunction and death. Thus, PCT is of great value for disease prognosis.\(^\text{[23]}\) sTREM-1 can be detected in body fluids when inflammatory reactions are present. sTREM-1 is hardly detected when no bacterial infection is present. As with PCT, sTREM-1 can also be used to identify whether ARDS is induced by infectious diseases.\(^\text{[24]}\) However, some researchers believe that its specificity and sensitivity are relatively low.\(^\text{[25]}\) Because of STREM-1’s high negative predictive value, most studies suggest that it has a higher value for non-infectious inflammation and it is of relatively great value in excluding ARDS caused by infectious factors.

Ferritin

Serum ferritin, C-reactive protein, ceruloplasmin, fibrin, etc. are the acute phase proteins. It is relatively convenient to measure ferritin clinically, yet researches on ferritin are inadequate. Elevated serum ferritin level in ALI and/or ARDS is due to expanded oxidative stress, increased release of pro-inflammatory cytokines, and worsened lung tissue injuries. Hence, ferritin could be used as an indicator of the occurrence and severity of ALI and/or ARDS. Connelly et al.\(^\text{[26]}\) have shown that ferritin levels are not in a linear relationship with C-reactive protein levels and stand no significant relationship with liver function. However, in the high-risk population for ALI and/or ARDS, high ferritin levels suggest that it is more likely to develop ALI and/or ARDS. Sharkey et al.\(^\text{[27]}\) have demonstrated that ferritin levels are positively correlated with ALI and/or ARDS morbidity and multiple organ failure among the high-risk population for ALI and/or ARDS, but it has no definite relationship with the oxygenation index, duration of mechanical ventilation or with mortality rate. In a controlled study of rats on a normal diet versus rats on a decreased iron diet, it was found that as the serum ferritin levels increase, the rats on iron-deficiency diet stood a high risk for hemorrhage, increased number of white blood cells in the lung lavage fluid, increased lung myeloperoxidase activity and elevated protein concentration in the lung lavage fluid.

References


