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LEVEL OF HYPOXEMIA AND LACTATE IN PNEUMONIA: A SIGNIFICANT INDICATOR OF DISEASE DYNAMICS, SEVERITY AND ENCEPHALOPATHY RISK

Pneumonia is the leading infectious cause of mortality worldwide and one of the most common lower respiratory tract infections that is contributing significantly to the burden of antibiotic consumption. Due to the complexity of its pathophysiology, it is widely accepted that clinical diagnosis and prognosis are inadequate for the accurate assessment of the severity of the disease. The most challenging task for a physician is the risk stratification of patients with community-acquired pneumonia **[1]**.

The pathological basis of severe pneumonia infection is the triggering of a series of inflammatory events, including inflammatory cytokine release, which results in hemodynamic changes. For example, elevated endotoxin levels in the blood and an uncontrolled systemic inflammatory response leads to multiple organ failure. Changes to the *in vivo* microenvironment and normal metabolic disorder caused by cells due to a lack of oxygen are the main reasons for the formation of multiple organ dysfunction syndrome. CRP is a product of fibrin dissolution, and is increased in inflammatory diseases. Therefore, the protein can be used as an important index to evaluate systemic inflammation. In patients with severe pneumonia, tissue organ effective blood volume reduction, which further exacerbates tissue hypoxia and increases anaerobic metabolism **[2]**.

The measured levels of biomarkers should be interpreted cautiously and always be correlated with clinical findings as many confounding factors should be taken into consideration for interpretation. Factors like age, antibiotic pretreatment, chronic hepatic disease, corticosteroids, renal impairment, and viral confection can critically affect some biomarker levels and thus their

sensitivity and specificity regarding treatment failure and clinical stability. Hence, results should be interpreted in line with the clinical presentation, and they should never substitute clinical judgment **[1]**.

Blood lactic acid is a product of the anaerobic glycolysis of glucose, and can directly reflect the tissue hypoperfusion and hypoxia conditions. Lactic acidosis is an important index of shock, hypoxia and oxygen metabolism, and quantitative detection and monitoring of the lactic acid levels in patients undergoing recovery from severe pneumonia is an important indicator, with significant value for assessment of the disease **[2]**.

In emergency and critical care medicine, serum lactate and its kinetics are useful parameters for critically ill patients as a marker of severity of illness. A significant advantage is that the determination of serum lactate is widely and rapidly available as a point-of-care measurement. Hyperlactatemia is an indicator of physiological stress, and anaerobic metabolism, and a "powerful predictor of mortality". Under stress conditions, lactate has been suggested to act as a biofuel that eliminates blood glucose use and provides additional glucose. Therefore, hyperlactatemia may indicate a protective response to stress under critical conditions **[9]** .

Basically, lactate can be used for two purposes. It can be used both for risk stratification and to monitor the response to therapy. Elevated lactate is a diagnostic criterion for septic shock following the sepsis-3 consensus. Lactate "clearance" is a target parameter for volume substitution in the absence of major liver dysfunction **[9]** .

The physiological basis for lactate clearance presumes that circulatory shock causes inadequate oxygen delivery, resulting in mitochondrial hypoxia. Under hypoxic conditions, mitochondrial oxidative phosphorylation fails, and energy metabolism becomes dependent on anaerobic glycolysis. Anaerobic glycolysis sharply increases the production of cellular lactate, which diffuses into the blood during prolonged cell hypoxia **[8.10]**.

The study of the problem of hypoxia in recent years is relevant, given the damage caused by coronavirus infection, which affects not only the respiratory tract, but leads to complications associated with hypoxic conditions affecting the central nervous and cardiovascular systems **[10]** .

Pneumonia caused by the SARS-CoV-2 virus presents with fever, dyspnea, and acute respiratory symptoms which can lead to refractory pulmonary failure. It is common among COVID-19 patients to develop acute respiratory distress syndrome (ARDS), a life-threatening form of respiratory failure.The severity of the condition of patients with COVID-19 is due to damage not only to the respiratory system, but also to the cardiovascular, central nervous system (CNS), kidneys, liver, as well as the severity of the immune response **[10]** .

Vassiliou et al. measured blood lactate at ICU admission and then every day until day 14. Although these authors found that the time course of blood

lactate values mirrored organ dysfunction, frank hyperlactatemia (i.e., >2 mmol/L) was prevalently found only before death, but still only present in less than half (i.e., 45%) of all patients who died with SARS-CoV-2 infection. Further important evidence comes from the study of Lardaro et al., who retrospectively evaluated 542 COVID-19 patients with bacterial co-infection. In these patients, despite the fact that bacteremia was significantly associated with elevated blood lactate values, the clinical outcomes did not significantly differ between patients with and without bacteremia **[7]**.

Lemeshevskaya et al. evaluated 100 patient cases with COVID-19 and found, the level of blood lactate in pneumonia associated with COVID-19 is significantly higher with increased severity of the disease and is associated with an increase in hypoxia, damage to the central nervous system causing dyscirculatory encephalopathy and other changes. In their study, patients with severe viral-bacterial pneumonia exhibited older age, a higher proportion of women, and more severe acute respiratory failure, reflected by elevated lactate levels. Additionally, these patients showed a higher prevalence of encephalopathy of varying severity. Among 24 patients with dyscirculatory encephalopathy, severity impacted their ability to position and use an oxygen mask. Severe pneumonia cases had higher lactate levels, with survivors at 2.5 mmol/l and deceased at 3.6 mmol/l, compared to moderate cases at 2.2 mmol/l **[10]**.

Pulse oximetry is a widely used noninvasive technology for monitoring oxygen saturation in various clinical settings, but it does not provide information about acid-base balance or alveolar ventilation. Acid-base balance is critical for assessing overall respiratory and metabolic health. Blood gas analysis is the gold standard method for determining arterial oxygen saturation and provides information on pH, partial pressure of carbon dioxide, partial pressure of oxygen, lactate and bicarbonate levels, allowing for a comprehensive assessment of acid-base balance. Therefore, it is essential to consider the acid-base status of the blood when interpreting pulse oximetry readings **[3]**. Pulse oximeter readings are influenced by temperature, blood pH, and PaCO2 levels, impacting hemoglobin's oxygen binding and release. Alkalosis and low temperature lead to overestimated oxygen saturation, while acidosis and high temperature reduce it. Hypocapnia and alkalosis maintain high oxygen saturation, while hypercapnia and acidosis decrease oxygen release in tissues, requiring higher PaO2 for hemoglobin saturation **[10]** .

CRP also has some reported use in the hyperacute COVID-19 phenotype. Manson et al identified a significant subgroup of patients presenting to two tertiary hospitals in the UK in March 2020, where CRP >150 mg/L or doubling from 50 mg/L within 24 hours was strongly predictive of death or the need for intubation within the following 24 hours. A further analysis from South Korea reported that an admission CRP >80 mg/L had a higher sensitivity for predicting adverse outcome in COVID-19 than a NEWS score of 2 or more. There are

several limitations with using CRP as a monitor for disease severity, because it has a lag time before rising **[4]**.

Several reviews and meta-analyses have reported the prognostic value of lactate dehydrogenase (LDH) for severity of COVID-19 and other inflammatory diseases. Serum LDH is a metabolic as well as a prognostic biomarker for immune surveillance. A high level of LDH has been related to respiratory function and a predictor of respiratory failure in COVID-19 patients. Its rise in serum is associated with poor outcomes in immunocompromised patients and appears to be linked to serum lactate, the end product of glycolysis. According to studies, LDH is the only best measure that may predict ICU admission or serum LDH levels in diabetic COVID-19 patients aged 70 or above predicted fatality **[4]** .

Procalcitonin is so far known as a marker of severe sepsis mostly caused by Gram-negative bacteria. But recent literature provided hints for its elevation after mechanic or hypoxic tissue damage, too **[5]**. Also respiratory viral infection can stimulate PCT production in the absence of bacterial pneumonia. This observation challenges the premise that PCT expression remains low during viral infection due to inhibitory IFN signalling. It also contradicts the corollary-that elevated PCT during viral illness indicates bacterial coinfection **[11]**.

The search results highlight the importance of biomarkers and techniques in diagnosing and assessing the severity of pneumonia, particularly in the context of hypoxia. The level of blood lactate in pneumonia associated with COVID-19 is significantly higher with severe severity of the disease and is associated with an increase in hypoxia, damage to the central nervous system and other changes. Novel biomarkers that can predict severity and treatment response are needed, as current biomarkers have limitations. Combining biomarkers with clinical scores or using them in a panel can increase diagnostic and predictive value, particularly in severely ill patients.

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