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Lactate dehydrogenase is associated with 28-day mortality in patients with sepsis: a retrospective observational study

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ABSTRACT

Background: Sepsis is a major health care problem, which affects millions of people around the world. Glucose metabolic reprogramming of immune cells plays a crucial role during advancement of sepsis. However, the association between glucose metabolic reprogramming and mortality in patients with sepsis is unclear. Lactate dehydrogenase (LDH) catalyzes the last step of glycolysis. Investigating the relationship between LDH and mortality is important to understand the effect of metabolic reprogramming on prognosis of patients with sepsis.

Methods: A total of 192 patients with sepsis were included in our study. Data on characteristics of patients, biochemical variables, and inflammatory mediator were collected. Association between the level of serum LDH and 28-day mortality was also analyzed. The correlations between serum LDH, interleukin-1β, creatinine, PaO_2/FiO_2, and lactate were also observed. The association between LDH and the risk of death was further analyzed. Moreover, receiver operating characteristic curve was depicted to compare the accuracy in prediction of LDH and other variables.

Results: There were statistic difference in 28-day mortality between elevated LDH group and normal LDH group ($P = 0.021$). Level of serum LDH was an independent risk factor for death of patients with sepsis (hazard ratio 1.005, 95% confidence interval 1.002-1.007, $P = 0.001$). There were significant correlations between LDH, interleukin-1β ($r = 0.514$, $P = 0.000$), creatinine ($r = 0.368$, $P = 0.000$), PaO_2/FiO_2 ($r = -0.304$, $P = 0.000$), and lactate ($r = 0.560$, $P = 0.000$). The receiver operating characteristic curves showed that the area under the LDH curve for prediction for mortality was 0.783.

Conclusions: Serum LDH is probably associated with 28-day mortality in patients with sepsis.

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Introduction

Sepsis is defined as life-threatening organ dysfunction due to a dysregulated host response to infection.[1] It is suggested that the quick sequential [sepsis-related] organ failure assessment (qSOFA) is statistically greater than sequential [sepsis-related] organ failure assessment (SOFA) and systematic inflammatory respiratory syndrome (SIRS) in evaluating the predictive validity for in-hospital mortality for patients with suspected infection outside of the intensive care unit (ICU).[2] Several studies have demonstrated that the conversion of cellular metabolism of glucose plays a crucial role in the function cells of the immune system in the sepsis model. After lipopolysaccharide stimulation, the metabolism of glucose by the immune cells shifts from citrate cycle, also called tricarboxylic acid cycle (TCA), to aerobic glycolysis.[3-6] The change of glucose metabolism is known as glucose metabolic reprogramming. Inflammatory mediators such as interleukin-1β (IL-1β) are produced rapidly by immune cells on the basis of glucose metabolic reprogramming.[6,7] On the other hand, as a metabolic product of aerobic glycolysis, a mass of lactate accumulates during the glucose metabolic reprogramming process.[8] Inflammatory mediators and lactate together contribute to the progress of sepsis. Nevertheless, the qSOFA criteria do not involve the metabolic status of the patients with sepsis or septic shock. Lactate dehydrogenase (LDH) may catalyze the conversion of pyruvate to lactate reversibly, which is the last step of aerobic glycolysis. In this study, we selected lactic dehydrogenase, which is a common biochemical marker, to confirm the relationship between glucose metabolic reprogramming and mortality in patients with sepsis. We primarily observed the correlation between serum LDH and 28-day mortality in patients admitted to ICU, who were diagnosed with sepsis. We also assessed the association between LDH, lactate, and inflammatory mediators such as IL-1β. We attempted to provide a new insight by probing into the effect of metabolic reprogramming on prognosis of patients with sepsis.

Materials and methods

Study population

A total of 255 adult patients with sepsis or septic shock were admitted to the ICU from January 2014 to March 2017 at the Affiliated Hospital of Nanjing University of Chinese Medicine. These patients were enrolled in this study. Sepsis was diagnosed by using SIRS criteria[9] that included respiratory rate of 20/min or more or $PaCO_2$ of less than 32 mm Hg; white blood cell (WBC) of more than 12×10^9 or less than 4×10^9 or myelocytes count of more than 10%; heart rate of more than 90/min; and temperature of more than 38°C or less than 36°C. All the recruited patients were also associated with infection or suspected infection. Patients who had all the laboratory results were included in this study. Patients who were to be discharged from our hospital when they were still in critical illness condition were excluded. Patients who disagreed to provide their clinical data for the privacy reasons were also excluded from this study. Patients with sepsis or septic shock, who endured myocardial infarction, acute hepatitis, and malignant tumor, simultaneously, were also excluded for the reason that the diseases such as myocardial infarction, acute hepatitis, malignant tumor, and sepsis, both contribute to elevated serum level of LDH. According to the criteria, 255 adult patients were enrolled to accrue 192 study participants. The included patients were divided into normal LDH group and elevated LDH group according to the serum LDH level when admitted to ICU. The normal value of serum LDH was defined as less than 225 u/L. The elevated value of serum LDH was defined as 225 u/L or more. Figure 1 shows the flow diagram for the participants. The institutional review board at Affiliated Hospital of Nanjing University of Chinese Medicine approved the present study (2017NL-073-02) and waived the necessity to obtain written consent because of its retrospective nature.

Data collection

The general socioeconomic data, including sex, age, acute physiology and chronic health evaluation II (APACHE II), and SOFA, were recorded when the patients were admitted to the ICU. The biochemical data, including LDH, WBC, C-reaction protein (CRP), D-dimer, albumin, creatinine, oxygenation index (PaO_2/FiO_2), brain natriuretic peptide (BNP), lactate, and IL-1β, were selected for testing when the patients were diagnosed with sepsis or septic shock. We also recorded the source of infection and history of each patient. All the study patients were divided into two groups according to their serum LDH levels. The patients with normal serum LDH level (less than 225 u/L) were enrolled into normal LDH group, and the patients with elevated LDH level (225 u/L or more) were enrolled into elevated LDH group. The WBC and CRP were tested with hematology analyzer (Mindray, BC-1800). The serum LDH, albumin, and creatinine were tested with enzyme kinetic method (Beckman, AU5800). The PaO_2 was tested with blood gas analyzer (Radiometer, ABL 800). The D-dimer and IL-1β were tested with enzyme-linked immunosorbent assay. The BNP was tested with microparticle enzyme immunoassay (Roche, Cobas h 232). During the course of sepsis, the incidences of

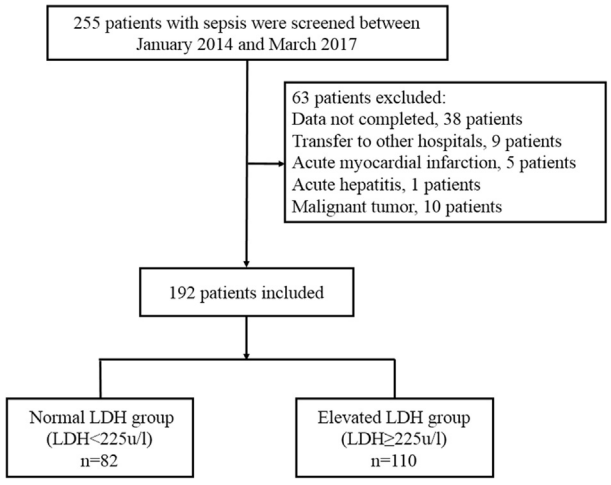

Fig. 1 – Flow chart of patient enrollment.