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Original Article

Correlation between serum 4-HNE and lactic acid levels and disease status in patients with severe pneumonia and its diagnostic value and prognostic evaluation

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Abstract: Purpose: To investigate the relationship between serum 4-Hydroxynonenal (4-HNE) and lactic acid (Lac) levels and the disease status of severe pneumonia (SP) patients, and to observe the value of serum 4-HNE and Lac in the prognosis assessment of SP patients. Methods: The clinical data of 76 patients with SP (SP group) and 76 patients with general pneumonia (GP group) in Shanghai Ninth People's Hospital from September 2020 to June 2022 were retrospectively collected. According to the survival status of SP patients 28 d after admission, they were divided into a survival group (49 cases) and a death group (27 cases). Serum 4-HNE and Lac levels were compared between groups. Pearson was used to observe the correlation between serum 4-HNE and Lac levels and SP disease status. Receiver operating characteristic curve was used to analyze the evaluation efficacy of serum 4-HNE and Lac levels. Results: The levels of serum 4-HNE and Lac in the SP group were higher than in the GP group ($P<0.05$). Serum 4-HNE and Lac levels in SP patients were positively correlated with CURB-65 score ($r=0.626$; $r=0.427$, $P<0.05$). The levels of serum 4-HNE and Lac in the death group were higher than survival group ($P<0.05$). Area under curve (AUC) of serum 4-HNE and Lac levels in the diagnosis of SP was 0.796 and 0.799 respectively. AUC for serum 4-HNE combined with Lac levels in the diagnosis of SP was 0.871. AUC of serum 4-HNE and Lac levels in predicting the prognosis of SP was 0.768 and 0.663 respectively. AUC of serum 4-HNE combined with Lac levels in predicting the prognosis of SP was 0.837. Conclusion: Serum 4-HNE and Lac levels in SP patients are significantly increased, and serum 4-HNE combined with Lac level has good application value in the early diagnosis and prognosis prediction of SP.

Keywords: Severe pneumonia, 4-Hydroxynonenal, lactic acid, disease status, prognosis

Introduction

Pneumonia is a common respiratory system disease seen the in clinic. However, due to many factors, some patients with pneumonia will have progressive aggravation of their condition, which leads to the occurrence of severe pneumonia (SP) [1]. SP is a common critical disease seen clinically. It can be caused by pathogen infection such as fungi, bacteria, and viruses. It may also be affected by factors such as advanced age, environment, and smoking [2]. The disease can lead to multiple organ function involvement in the whole body, and it easily develops into severe lesions such as septic shock, multiple organ dysfunction syndrome, and sepsis [3]. The disease is complicated and progresses rapidly, with a mortality rate of 30%-50%, which seriously endangers the life and health of patients [4]. At present, symptomatic treatment such as anti-infection treatment and vital sign support is mainly adopted for SP, but the prognosis of patients is still poor [5]. In clinical practice, white blood cell, C-reactive protein and other indicators can evaluate the severity and prognosis of SP, but they lack high sensitivity and specificity. Moreover, CURB-65, pneumonia severity index and other scoring systems are complicated and have certain limitations. Therefore, finding biological markers with high value in the diagnostic and prognostic evaluation of SP has become an urgent problem to be solved.

4-Hydroxynonenal (4-HNE), as a product of lipid peroxidation in the body during oxidative stress,

is considered to be one of the most powerful active aldehydes [6]. 4-HNE can reflect the abnormal condition of oxidation/anti-oxidation balance in patients, and participate in many cytotoxic processes such as protein dysfunction, apoptosis, and the occurrence and development of inflammatory reaction [7]. Abnormal increase of 4-HNE can induce nervous system diseases, cardiovascular injury, liver and lung injury in humans, and also affect energy metabolism [8]. Lactic acid (Lac) is a substance secreted by glycolysis during hypoxia. As an important indicator for monitoring blood perfusion and cell hypoxia, Lac widely exists in the metabolic process of human body and animals [9]. Lac can reflect the degree of tissue hypoxia and is a measure of oxygenation metabolism. The inactivation of rate-limiting enzymes, the high stress response of catecholamine and the weakening of tissue clearance will all increase the level of Lac [10].

At present, there are some clinical studies on the significance of 4-HNE and Lac monitoring and SP diagnosis, but studies on the severity of disease and survival of 4-HNE and Lac are relatively rare. The purpose of this study was to investigate the relationship between serum 4-HNE and Lac levels and the disease status of SP patients, and to observe the value of serum 4-HNE and Lac in the prognosis assessment of SP patients.

Materials and methods

Research subjects

The clinical data of 76 patients in the SP group and 76 patients with general pneumonia (GP group) in Shanghai Ninth People's Hospital from September 2020 to June 2022 were retrospectively collected. According to the survival status of SP patients 28 d after admission, they were divided into a survival group (49 cases) and a death group (27 cases). Inclusion criteria: Compliance with relevant diagnostic criteria [11]. Main symptoms (met at least one condition): mechanical ventilation, septic shock; Secondary symptoms (met at least three conditions): respiratory rate ≥30 times/min, disorder of consciousness/orientation, oxygenation index ≤250 mmHg, multi-lobar infiltration, azotemia, white blood cell $<4.0 \times 10^9$/L, platelet count $<100 \times 10^9$/L, temperature <36°C, hypotension. Diagnosis was confirmed through examinations such as clinical symptoms and imaging examination. Patient information was complete. Exclusion criteria: Merger with other systemic infectious diseases; Combined with malignant tumor; Combined with immune system diseases and blood system diseases; Combined with tuberculosis. This research was approved by the Shanghai Ninth People's Hospital ethics committee.

Research methods

Five mL of peripheral venous blood was collected from all subjects on an empty stomach in the morning of the second day after admission, centrifuged at 3000 r/min for 10 min, and the serum was separated and stored at -20°C for further testing. Enzyme-linked immunosorbent assay was used to test the level of 4-HNE (E03H0203, Shanghai Lanji) and spectrophotometry was used to test the level of Lac (E1112821, Shanghai Biyou). The operation steps were performed strictly in accordance with the kit instructions.

Main observation index: The serum levels of 4-HNE and Lac between GP and SP groups were compared. The levels of serum 4-HNE and Lac between survival group and the death group were compared.

Secondary observation index: The general data of the GP group and SP group were collected. The correlation between serum 4-HNE, Lac levels and the disease status in the SP group was observed. The severity of the disease in the SP group was scored using CURB-65 score [12], including disorder of consciousness, blood urea nitrogen, respiratory rate, blood pressure, and age. One point for each item and 5 points for the total.

Statistical methods

SPSS 22.0 software was used for data analysis. Measurement data were expressed as mean ± standard deviation, and t test was used for comparison between groups. Counting data were expressed as ratio, and χ^2 test was used for comparison. Pearson was used for correlation analysis, and receiver operating characteristic curve (ROC) was used to analyze the evaluation efficacy of serum 4-HNE and Lac levels. $P<0.05$ meant the difference was statistically significant.

Table 1. General data (n, %, $\bar{x} \pm s$)

Group	Gender		Age (years)	Smoking history	Basic diseases		
	Male	Female			Coronary heart disease	Diabetes	Hypertension
GP group	41 (53.95%)	35 (46.05%)	54.04±3.75	29 (38.16%)	21 (27.63%)	23 (30.26%)	28 (36.84%)
SP group	43 (56.58%)	33 (43.42%)	53.86±3.80	32 (42.11%)	20 (26.32%)	25 (32.89%)	31 (40.79%)
χ^2/t value	0.106		0.293	0.246	0.033	0.122	0.249
P value	0.744		0.769	0.620	0.855	0.727	0.618

Note: GP: General Pneumonia; SP: Severe Pneumonia.

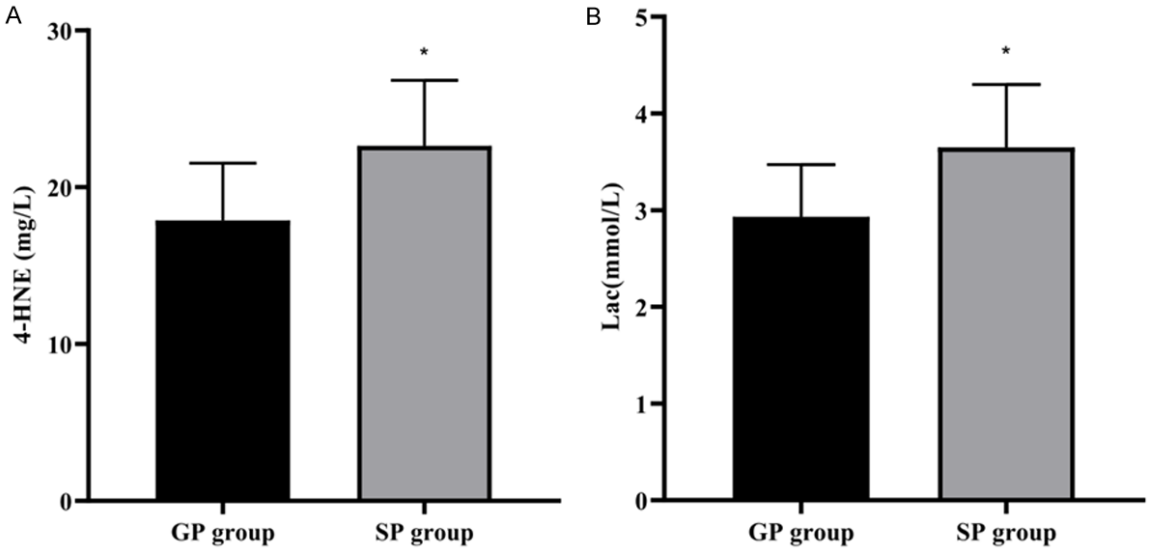

Figure 1. Comparison of serum 4-HNE and Lac level between GP group and SP group. A. Serum 4-HNE level; B. Serum Lac level. Compared with GP group, *P<0.05. Note: 4-HNE: 4-Hydroxynonenal; Lac: Lactic Acid; GP: General Pneumonia; SP: Severe Pneumonia.

Table 2. Correlation between serum 4-HNE and Lac levels and disease status in SP patients

Variable	CURB-65 score	
	r value	*P* value
4-HNE	0.626 (95% CI 0.465-0.746)	<0.0001
Lac	0.427 (95% CI 0.223-0.595)	0.0001

Note: 4-HNE: 4-Hydroxynonenal; Lac: Lactic Acid; SP: Severe Pneumonia.

Results

Comparison of general data between GP group and SP group

The data of gender, age, smoking history and basic diseases of the two groups were balanced and comparable (P>0.05). As shown in **Table 1**.

Comparison of serum 4-HNE and Lac level between GP group and SP group

Serum 4-HNE levels in GP group and SP group were (17.88±3.65) mg/L and (22.64±4.18) mg/L, respectively. Serum Lac levels in SP group and GP group were (2.93±0.54) mmol/L and (3.65±0.65) mmol/L, respectively. The levels of serum 4-HNE and Lac in the SP group were higher than GP group (P<0.05). As shown in **Figure 1**.

Correlation between serum 4-HNE and Lac levels and disease status in SP patients

Serum 4-HNE and Lac levels in SP patients were positively correlated with CURB-65 score (r=0.626; r=0.427, P<0.05). As shown in **Table 2**.

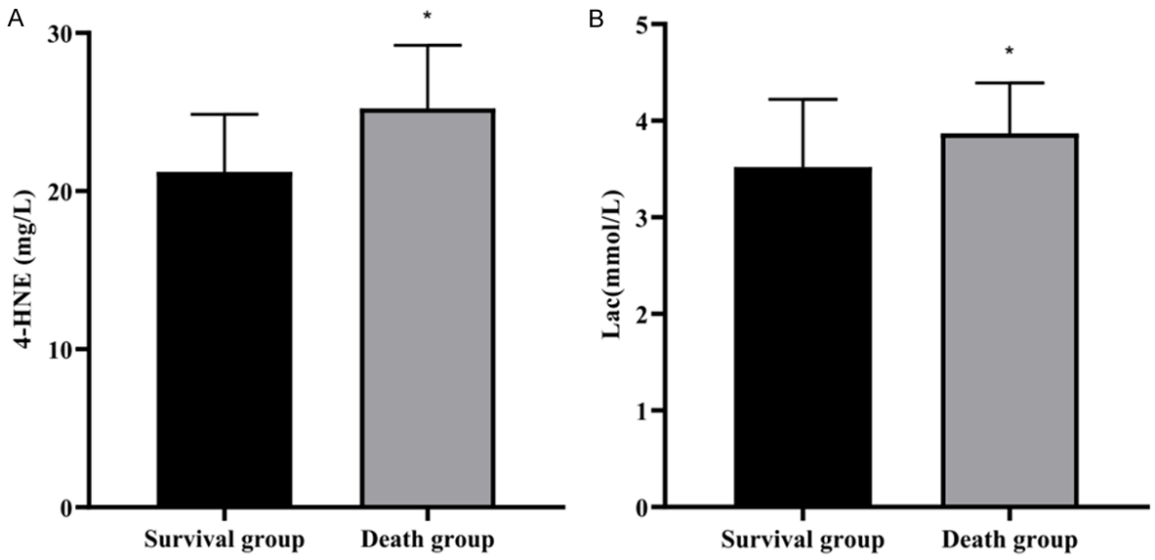

Figure 2. Comparison of serum 4-HNE and Lac level between survival group and death group. A. Serum 4-HNE level; B. Serum Lac level. Compared with the survival group, *P<0.05. Note: 4-HNE: 4-Hydroxynonenal; Lac: Lactic Acid.

Table 3. Diagnostic efficacy of serum 4-HNE and Lac levels in SP patients

Variable	AUC	Standard error	Progressive Sig.	Asymptotic 95% confidence interval	
				Lower limit	Upper limit
4-HNE	0.796	0.035	0.000	0.727	0.865
Lac	0.799	0.036	0.000	0.729	0.868
4-HNE+Lac	0.871	0.028	0.000	0.816	0.926

Note: 4-HNE: 4-Hydroxynonenal; Lac: Lactic Acid; SP: Severe Pneumonia; AUC: Area Under Curve.

Comparison of serum 4-HNE and Lac level between survival group and death group

Serum 4-HNE levels in survival group and death group were (21.22±3.63) mg/L and (25.23±3.99) mg/L, respectively. Serum Lac levels in survival group and death group were (3.52±0.70) mmol/L and (3.87±0.52) mmol/L, respectively. The levels of serum 4-HNE and Lac in the death group were higher than survival group (P<0.05). As shown in **Figure 2**.

Diagnostic efficacy of serum 4-HNE and Lac levels in SP patients

Area under curve (AUC) for serum 4-HNE levels in the diagnosis of SP was 0.796 (95% CI: 0.727-0.865). AUC for serum Lac levels in the diagnosis of SP was 0.799 (95% CI: 0.729-0.868). AUC for serum 4-HNE combined with Lac levels in the diagnosis of SP was 0.871 (95% CI: 0.816-0.926). As shown in **Table 3**; **Figure 3**.

Predictive efficacy of serum 4-HNE and Lac levels on the prognosis of SP patients

AUC of serum 4-HNE levels in predicting the prognosis of SP was 0.768 (95% CI: 0.656-0.880). AUC of serum Lac levels in predicting the prognosis of SP was 0.663 (95% CI: 0.539-0.786). AUC of serum 4-HNE combined with Lac levels in predicting the prognosis of SP was 0.837 (95% CI: 0.739-0.935). As shown in **Table 4**; **Figure 4**.

Discussion

In recent years, with the aggravation of aging population and abuse of antibiotics, the incidence of pneumonia is increasing, and some GP patients can progress to SP patients, which aggravates the economic burden of patients [13]. SP has the characteristics of rapid onset and high mortality, mainly manifested as fever, cough, decreased blood pressure, respiratory failure, and even death in severe cases [14].

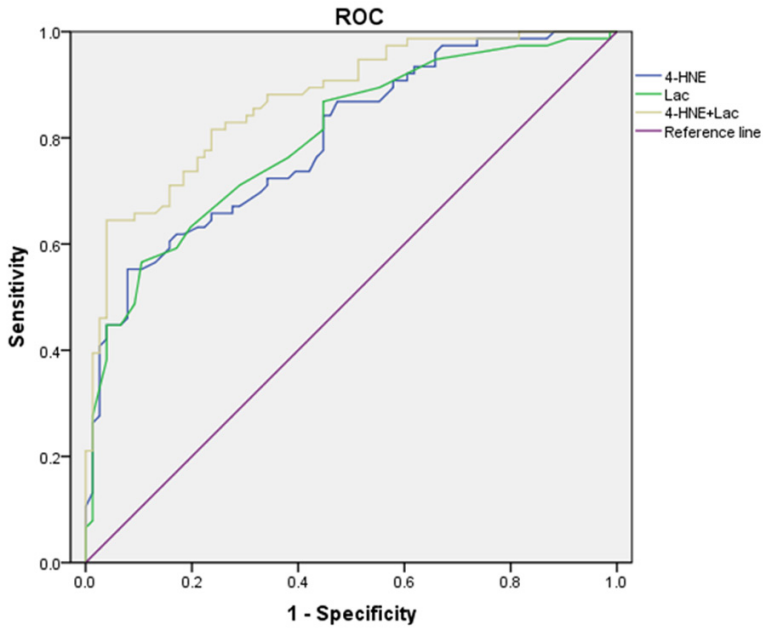

Figure 3. Diagnostic efficacy of serum 4-HNE and Lac levels in SP patients. Note: 4-HNE: 4-Hydroxynonenal; Lac: Lactic Acid; ROC: Receiver Operating Characteristic.

Table 4. Predictive efficacy of serum 4-HNE and Lac levels on the prognosis of SP patients

Variable	AUC	Standard error	Progressive Sig.	Asymptotic 95% confidence interval	
				Lower limit	Upper limit
4-HNE	0.768	0.057	0.000	0.656	0.880
Lac	0.663	0.063	0.019	0.539	0.786
4-HNE+Lac	0.837	0.050	0.000	0.739	0.935

Note: 4-HNE: 4-Hydroxynonenal; Lac: Lactic Acid; SP: Severe Pneumonia; AUC: Area Under Curve.

Therefore, mastering the early evaluation indexes of SP is especially important for disease control and prognosis improvement.

4-HNE is an oxygen-containing unsaturated aldehyde, which is one of the most stable terminal representative products of lipid peroxidation, and can reflect the oxidative stress response in the lung [15]. 4-HNE has been confirmed to be highly expressed in the airway, alveolar epithelial cells, vascular endothelial cells, neutrophils and macrophages [16, 17]. Kovacevic S et al. found that rats with acute renal injury in an ischemic state had high expression of 4-HNE, and the expression level of 4-HNE decreased with the improvement of renal function. Kovacevic S et al. found that rats with acute kidney injury under an ischemic state had high expression of 4-HNE, and the expression level of 4-HNE was decreased with the improvement of renal function [18]. Lou B et al. reported that elevated serum 4-HNE was an upstream metabolite regulating hyperglycemia, which was closely related to the occurrence and disease progression of type 2 diabetes [19]. The results of this study are similar to those of the above studies. We found that the serum 4-HNE level of SP group was higher than in the GP group, and the 4-HNE level in the death group was higher than survival group. Besides, the serum 4-HNE level of SP patients was positively correlated with CURB-65 score. This suggests that monitoring serum 4-HNE levels is helpful for the diagnosis of SP and prognosis evaluation. The possible reason is that: inflammatory reaction and oxidative stress reaction play an important role in the occurrence and development of SP. Under oxidative stress, the endogenous antioxidant system is affected, and 4-HNE begins to accumulate, which leads to lung tissue damage. The accumulation of 4-HNE is mainly induced by reactive oxygen species and other free radicals, which are involved in a variety of cytotoxic processes that have adverse effects on the body [20]. 4-HNE not only mediates a variety of signal pathways in the body and reacts with enzymes and kinases in a variety of cellular pathways, but also stimulates the expression of inflammatory factors, which in turn aggravates the inflammatory response and promotes the development of pneumonia [21]. In addition, 4-HNE can form adducts with multiple mitochondrial targets, resulting in mitochondrial dysfunction, destruction of cell energy metabolism and aggravation of lung injury in patients [22].

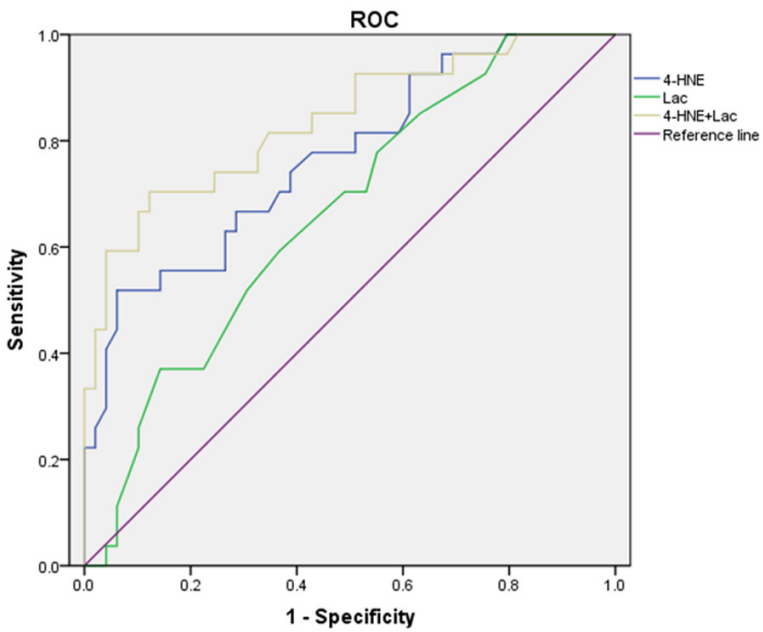

Figure 4. Predictive efficacy of serum 4-HNE and Lac levels on the prognosis of SP patients. Note: 4-HNE: 4-Hydroxynonenal; Lac: Lactic Acid; ROC: Receiver Operating Characteristic.

Glucose can undergo anaerobic metabolism through the glycolytic pathway to produce pyruvic acid, which is finally converted into Lac. The level of serum Lac can directly reflect the hypoperfusion of organ tissues and cell hypoxia [23]. Glycolysis is a metabolic pathway that widely exists in cells, and Lac can be produced by skeletal muscle cells, brain cells, red blood cells, skin and other histiocytes in the body [24]. Zhang W et al. analyzed hepatitis B positive patients and found that Lac level was higher in patients. Monitoring Lac level has some application value in the diagnosis of liver disease [25]. Innocenti F et al. found that Lac levels were higher in shock patients than in non-shock sepsis patients, and Lac levels were associated with the risk of death in sepsis patients [26]. Liu W et al. believe that SP patients have decreased enzyme activity, hypoperfusion of organ tissues, severe hypoxia of lung tissue cells, and decreased mitochondrial oxygen transport, which in turn cause an increase in serum Lac level. When lung tissue is damaged, the conversion rate of fibrin will be accelerated, causing the body to release more Lac [27]. With a more serious degree of hypoxia, the more serious the inter-tissue perfusion, the higher the content of Lac, and will even eventually lead to the occurrence of hyperlactatemia. We found that the serum Lac levels in the SP group and the death group were higher, and at the same time, Lac had a certain correlation with the disease status of SP. The results showed that serum Lac level could be used as one of the indicators for evaluating the severity and prognosis of SP. This is roughly consistent with Liu W's research results.

In addition, the ROC curve showed that the AUC of serum 4-HNE and Lac levels in the diagnosis of SP were 0.796 and 0.799 respectively. AUC for serum 4-HNE combined with Lac levels in the diagnosis of SP was 0.871. AUC of serum 4-HNE and Lac levels in predicting the prognosis of SP were 0.768 and 0.663 respectively. AUC of serum 4-HNE combined with Lac levels in predicting the prognosis of SP was 0.837. AUC predicted by the combination of 4-HNE and Lac was significantly higher than that predicted by a single index, which plays a synergistic role. The results of ROC analysis suggested that the serum levels of 4-HNE combined with Lac had good application value in the early diagnosis and prognosis prediction of SP. Clinically, the disease severity and prognosis of SP can be evaluated early by the combined detection of the two, so as to reduce damage from disease and risk of death in SP patients.

Conclusion

In summary, serum 4-HNE and Lac levels in SP patients are significantly increased, and serum 4-HNE combined with Lac level has good application value in the early diagnosis and prognosis prediction of SP. There are some limitations in this study: this is a retrospective study that has certain bias in case selection. In addition, the number of subjects included in this study was small, which may affect the results of the trial. Therefore, we need to conduct a large-sample, multi-center prospective study, and further verify the accuracy and applicability of the research results.

Disclosure of conflict of interest

None.

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References

[1] Martin-Loeches I and Torres A. New guidelines for severe community-acquired pneumonia. Curr Opin Pulm Med 2021; 27: 210-215.

[2] Phua J, Dean NC, Guo Q, Kuan WS, Lim HF and Lim TK. Severe community-acquired pneumonia: timely management measures in the first 24 hours. Crit Care 2016; 20: 237.

[3] Wang J and Song YL. Advances in severe community-acquired pneumonia. Chin Med J (Engl) 2019; 132: 1891-1893.

[4] Russell FM, Reyburn R, Chan J, Tuivaga E, Lim R, Lai J, Van HMT, Choummanivong M, Sychareun V, Khanh DKT, de Campo M, Enarson P, Graham S, La Vincente S, Mungan T, von Mollendorf C, Mackenzie G and Mulholland K. Impact of the change in WHO's severe pneumonia case definition on hospitalized pneumonia epidemiology: case studies from six countries. Bull World Health Organ 2019; 97: 386-393.

[5] Rello J and Perez A. Precision medicine for the treatment of severe pneumonia in intensive care. Expert Rev Respir Med 2016; 10: 297-316.

[6] Jaganjac M, Milkovic L, Gegotek A, Cindric M, Zarkovic K, Skrzydlewska E and Zarkovic N. The relevance of pathophysiological alterations in redox signaling of 4-hydroxynonenal for pharmacological therapies of major stress-associated diseases. Free Radic Biol Med 2020; 157: 128-153.

[7] Breitzig M, Bhimineni C, Lockey R and Kolliputi N. 4-Hydroxy-2-nonenal: a critical target in oxidative stress? Am J Physiol Cell Physiol 2016; 311: C537-C543.

[8] Zhong H and Yin H. Role of lipid peroxidation derived 4-hydroxynonenal (4-HNE) in cancer: focusing on mitochondria. Redox Biol 2015; 4: 193-199.

[9] Liu Z, Meng Z, Li Y, Zhao J, Wu S, Gou S and Wu H. Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with Sepsis. Scand J Trauma Resusc Emerg Med 2019; 27: 51.

[10] Gong C, Jiang Y, Tang Y, Liu F, Shi Y, Zhou H and Xie K. Elevated serum lactic acid level is an independent risk factor for the incidence and mortality of sepsis-associated acute kidney injury. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2022; 34: 714-720.

[11] Cao B, Huang Y, She DY, Cheng QJ, Fan H, Tian XL, Xu JF, Zhang J, Chen Y, Shen N, Wang H, Jiang M, Zhang XY, Shi Y, He B, He LX, Liu YN and Qu JM. Diagnosis and treatment of community-acquired pneumonia in adults: 2016 clinical practice guidelines by the Chinese Thoracic Society, Chinese Medical Association. Clin Respir J 2018; 12: 1320-1360.

[12] Ilg A, Moskowitz A, Konanki V, Patel PV, Chase M, Grossestreuer AV and Donnino MW. Performance of the CURB-65 score in predicting critical care interventions in patients admitted with community-acquired pneumonia. Ann Emerg Med 2019; 74: 60-68.

[13] Torres A, Chalmers JD, Dela Cruz CS, Dominedò C, Kollef M, Martin-Loeches I, Niederman M and Wunderink RG. Challenges in severe community-acquired pneumonia: a point-of-view review. Intensive Care Med 2019; 45: 159-171.

[14] Mizgerd JP. Pathogenesis of severe pneumonia: advances and knowledge gaps. Curr Opin Pulm Med 2017; 23: 193-197.

[15] Zabłocka-Słowińska K, Płaczkowska S, Skórska K, Prescha A, Pawełczyk K, Porębska I, Kosacka M and Grajeta H. Oxidative stress in lung cancer patients is associated with altered serum markers of lipid metabolism. PLoS One 2019; 14: e0215246.

[16] Galam L, Failla A, Soundararajan R, Lockey RF and Kolliputi N. 4-hydroxynonenal regulates mitochondrial function in human small airway epithelial cells. Oncotarget 2015; 6: 41508-41521.

[17] Chacko BK, Wall SB, Kramer PA, Ravi S, Mitchell T, Johnson MS, Wilson L, Barnes S, Landar A and Darley-Usmar VM. Pleiotropic effects of 4-hydroxynonenal on oxidative burst and phagocytosis in neutrophils. Redox Biol 2016; 9: 57-66.

[18] Kovacevic S, Ivanov M, Zivotic M, Brkic P, Miloradovic Z, Jeremic R, Mihailovic-Stanojevic N, Vajic UJ, Karanovic D, Jovovic D and Nesovic Ostojic J. Immunohistochemical analysis of 4-HNE, NGAL, and HO-1 tissue expression after apocynin treatment and hbo preconditioning in postischemic acute kidney injury induced in spontaneously hypertensive rats. Antioxidants (Basel) 2021; 10: 1163.

[19] Lou B, Boger M, Bennewitz K, Sticht C, Kopf S, Morgenstern J, Fleming T, Hell R, Yuan Z, Nawroth PP and Kroll J. Elevated 4-hydroxynonenal induces hyperglycaemia via Aldh3a1 loss in zebrafish and associates with diabetes progression in humans. Redox Biol 2020; 37: 101723.

[20] Jiang YL, Liu HY, Tang MM, Cheng JY, Zhao H and Fu L. Serum level of 4-hydroxynonenal in community-acquired pneumonia: a potential biomarker for severity and prognosis. Front Med (Lausanne) 2022; 9: 798343.
[21] Reyes-Jiménez E, Ramírez-Hernández AA, Santos-Álvarez JC, Velázquez-Enríquez JM, Pina-Canseco S, Baltiérrez-Hoyos R and Vásquez-Garzón VR. Involvement of 4-hydroxy-2-nonenal in the pathogenesis of pulmonary fibrosis. Mol Cell Biochem 2021; 476: 4405-4419.
[22] Xiao M, Zhong H, Xia L, Tao Y and Yin H. Pathophysiology of mitochondrial lipid oxidation: role of 4-hydroxynonenal (4-HNE) and other bioactive lipids in mitochondria. Free Radic Biol Med 2017; 111: 316-327.
[23] Gwak MH, Jo S, Jeong T, Lee JB, Jin YH, Yoon J and Park B. Initial serum lactate level is associated with inpatient mortality in patients with community-acquired pneumonia. Am J Emerg Med 2015; 33: 685-690.
[24] Demirel B. Lactate levels and pneumonia severity index are good predictors of in-hospital mortality in pneumonia. Clin Respir J 2018; 12: 991-995.
[25] Zhang W, Chen Z, Xue C, Zhang Y, Wu L, Zhu J, Xuan S, Tian J and Pang Z. The applicability of ADA, AFU, and LAC in the early diagnosis and disease risk assessment of hepatitis B-associated liver cirrhosis and hepatocellular carcinoma. Front Med (Lausanne) 2021; 8: 740029.
[26] Innocenti F, Meo F, Giacomelli I, Tozzi C, Ralli ML, Donnini C, Tassinari I, Caldi F, Zanobetti M and Pini R. Prognostic value of serial lactate levels in septic patients with and without shock. Intern Emerg Med 2019; 14: 1321-1330.
[27] Liu W, Peng L and Hua S. Clinical significance of dynamic monitoring of blood lactic acid, oxygenation index and C-reactive protein levels in patients with severe pneumonia. Exp Ther Med 2015; 10: 1824-1828.