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Prognostic value of T-lymphocyte subsets, lymphocyte-to-high-density lipoprotein ratio, interleukin 6, C-reactive protein and procalcitonin in patients with septic shock and effects of vitamin C on patients with septic shock

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Abstract: **Background**: Septic shock remains a critical condition with high mortality, necessitating reliable prognostic biomarkers and effective adjunct therapies. **Objectives**: This study explored prognostic biomarkers and the effect of vitamin C in septic shock. **Methods**: This study analyzed 110 patients (January 2023-March 2024), stratified by 28-day outcome into survival (n=90) and death (n=20) groups. Compared to survivors, the death group exhibited significantly lower lymphocyte-to-high-density lipoprotein ratio (LHR), CD3+, CD3+CD4+, CD4+/CD8+ and higher interleukin 6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT), CD3+CD8+. **Results**: The receiver operating characteristic analysis showed the combination of LHR, IL-6, CRP, PCT and CD4+/CD8+ predicted death best [area under the receiver operating characteristic curve (AUC) =0.960], outperforming single markers. Patients were randomized to control (hydrocortisone) or observation (hydrocortisone with vitamin C) group. Post-treatment, both groups showed improved mean arterial pressure (MAP), central venous pressure (CVP) (increased), heart rate (HR) (decreased) and reduced PCT, tumor necrosis factor-α (TNF-α), IL-6 and Sequential Organ Failure Assessment (SOFA) score; however, improvements were significantly greater in the vitamin C group. **Conclusion**: The combination of LHR, IL-6, CRP, PCT and CD4+/CD8+ has prognostic value. Vitamin C adjunct therapy significantly enhances hemodynamic improvement, reduces inflammation, lowers SOFA scores and improves prognosis in septic shock patients.

Keywords: C-reactive protein; Interleukin 6; Lymphocyte-to-high-density lipoprotein ratio; Procalcitonin; Prognosis; Septic shock; T-lymphocyte subsets; Vitamin C

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INTRODUCTION

Infectious shock, also known as septic shock, is a common disease in intensive care medicine (Srzić *et al*., 2022). Sepsis is defined as a systemic inflammatory response to severe infection; when it evolves into septic shock, circulatory failure and metabolic derangements ensue, leading to a sharp rise in mortality (Ford *et al*., 2025). National data indicate that septic shock claims over 19 million lives annually in China, with case-fatality surpassing 40%; among survivors, persistent organ dysfunction or cognitive deficits are common (Xie *et al*., 2020). Growing scholarly focus now targets early intervention and prognostic markers for septic shock to guide clinicians and curb mortality (Gu *et al*., 2020, Srzić *et al*., 2022).

Emerging evidence indicates that the immune function of septic shock patients is affected and the level of T lymphocytes changes accordingly (Mouillaux *et al*., 2019). Procalcitonin (PCT), the precursor peptide of calcitonin, demonstrates rapid elevation during bacterial infections due to systemic inflammatory responses (Wussler *et al*., 2019). C-reactive protein (CRP), an acute-phase reactant, surges during bacterial invasion or tissue injury to modulate cellular responses (Puthucheary *et al*., 2022). Interleukin-6 (IL-6) is a pleiotropic cytokine that serves as a key mediator in the human inflammatory cascade, orchestrating both pro-inflammatory and anti-inflammatory responses (Li *et al*., 2025). Current evidence consistently links these biomarkers to septic-shock onset and severity (Song *et al*., 2019). Lipopolysaccharide (LPS), the predominant endotoxin released during sepsis, acts as a pivotal trigger that initiates and amplifies the cascade leading to septic shock (Gu *et al*., 2023). Evidence indicates that, in septic shock, circulating lipoproteins scavenge bacterial pathogens early in inflammation, promote subsequent tissue repair and neutralize LPS, collectively dampening the inflammatory response (Foster and Kellum, 2023). Among plasma lipoproteins, high-density lipoprotein (HDL) exhibits the strongest affinity for LPS binding and detoxification (Han *et al*., 2021). In septic shock, circulating HDL drops markedly and this decline mirrors both disease severity and prognosis (Tanaka *et al*., 2019). Besides, the lymphocyte-to-high-density lipoprotein ratio (LHR) has emerged as a novel inflammatory indicator (Liu *et al*., 2023). Emerging evidence identifies the LHR as a reliable prognostic indicator for metabolic syndrome, reflecting its strong association with systemic inflammation (Chen *et al*., 2019).

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The current therapeutic paradigm for septic shock encompasses source control, antimicrobial therapy, hemodynamic stabilization through fluid resuscitation and vasopressor support, along with comprehensive organ function maintenance (García-de-Acilu *et al*., 2021). Despite substantial advances in therapeutic interventions, septic shock continues to demonstrate persistently high mortality rates (Hernández *et al*., 2019). Exploring complementary therapeutic approaches to optimize septic shock management has gained significant research attention.

Ascorbic acid (vitamin C) functions as an essential water-soluble antioxidant and enzymatic cofactor, participating in numerous critical biochemical pathway (Böttger *et al*., 2021). In the pathophysiology of septic shock, vitamin C demonstrates pleiotropic benefits encompassing oxidative stress reduction, inflammatory modulation, hypothalamic-pituitary-adrenal axis support, nitric oxide metabolism regulation and catecholamine production potentiation (Fujii *et al*., 2022). In recent years, clinical study has reported that intravenous vitamin C administration attenuates sepsis-induced organ dysfunction and is associated with improved survival rates (Marik, 2018).

Herein, the objectives were twofold: first, to investigate the prognostic value of T-lymphocyte subsets, LHR, IL-6, CRP and PCT in septic shock patients; second, to quantify vitamin C's impact in patients with septic shock.

MATERIALS AND METHODS

General data

From January 2023 to March 2024, 110 septic shock patients admitted to the Affiliated Jiangning Hospital of Nanjing Medical University were chosen to be the study objects. Inclusion criteria: (1) patients meeting Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) diagnostic criteria for septic shock (Singer *et al*., 2016); (2) More than 18 years of age; (3) The patient signed the consent form. Exclusion criteria: (1) Shock caused by liver insufficiency, leukemia or other causes; (2) Patients suffered from neurological disease and was unable to cooperate with the study; (3) Combined pneumothorax and severe arrhythmia. This study analyzed 110 septic shock patients categorized by 28-day outcomes into survivors (n=90, 60 males and 30 females, mean age 68.21±15.60 years) and non-survivors (n=20, 12 males and 8 females, mean age 68.36±15.41 years). The groups showed comparable baseline characteristics ($p>0.05$), including similar hospitalization durations (survivors: 17.27±4.67 days; non-survivors: 17.32±4.04 days). For therapeutic evaluation, patients were randomized to control (n=55, 40 males, mean age 68.25±15.64 years) and vitamin C treatment groups (n=55, 32 males, mean age 68.32±15.43 years), with no significant demographic differences ($p>0.05$) and equivalent hospitalization periods (control: 17.30±4.68 days; treatment: 17.35±4.65 days).

Detection methods

Within 24 hours of hospital admission, fasting venous blood samples (5 mL) were collected, centrifuged for 10 min at 3000 r/min (centrifugation radius 10 cm) and stored in a refrigerator at 4℃ to be measured. Flow cytometry (Becton, Dickinson and Company, USA) was used to detect the proportion of CD^+T cells ($CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, as well as $CD4^+/CD8^+$) in lymphocytes. IL-6, CRP, along with PCT levels were examined by enzyme-linked immunosorbent assay (ELISA). Besides, all subjects were asked to conduct lipid test and LHR was calculated according to lymphocyte and HDL test results.

Treatment methods

Both groups were given resuscitation therapy such as fluid resuscitation, anti-inflammatory and blood purification. Patients in the control group were treated with hydrocortisone (Hubei Tiansheng Pharmaceutical Co., LTD.), intravenous drip, 200mg continuous intravenous infusion, once a day. Patients in the observation group were treated with hydrocortisone and vitamin C. The treatment of hydrocortisone was the same as the control group. Besides, patients were treated with vitamin C (Sichuan Meida Kanghuakang Pharmaceutical Co., Ltd.), intravenous drip, 2.0 g/time, twice a day. Patients in both groups were treated for 7 days.

Observation indicators

(1) LHR in 2 groups; (2) IL-6, CRP and PCT levels in 2 groups; (3) Levels T lymphocyte subsets in 2 groups; (4) Prognostic value of LHR, IL-6, CRP, PCT and $CD4^+/CD8^+$ single and combined tests in septic shock patients; (5) The hemodynamic indexes including mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP) were monitored by Mindray Electrocardiogram (ECG) monitor; (6) 6 ml of fasting venous blood was collected from the patients and the levels of tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 were measured by ELISA. The level of PCT was determined by double-antibody sandwich immunochemiluminescence assay; (7) The sepsis-related organ failure assessment (SOFA) was used to score the respiratory, blood clotting, liver, circulatory, nervous and kidney systems of the patients, with 0 to 4 points for each item (Hagel *et al*., 2022). The higher the score was, the more severe the organ failure and the worse the prognosis.

Statistical analysis

All analyses were performed with Statistical Package for the Social Sciences (SPSS) 21.0. Continuous variables were presented as mean ± SD and compared using the independent-samples t-test. Categorical variables were summarized as counts (percentages) and compared using the χ^2 test. Receiver operating characteristic (ROC) curves were generated to evaluate the prognostic utility of LHR, IL-6, CRP, PCT and T-lymphocyte subsets, with areas under the curves (AUCs) compared non-parametrically; significance was set at $P < 0.05$.

RESULTS

LHR in 2 groups

In contrast to the survival group, the level of LHR was declined in the death group (P<0.01, Fig. 1).

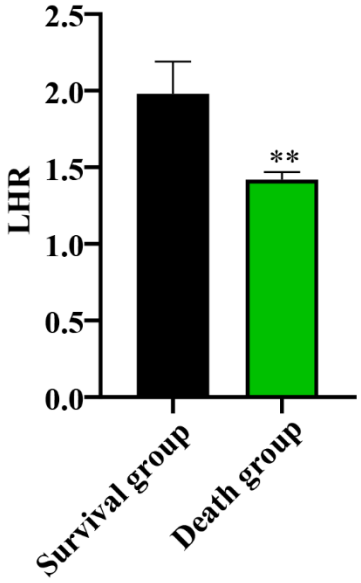

Fig. 1: Levels of LHR in survival and death groups.
**P<0.01; LHR: lymphocyte-to-high-density lipoprotein ratio.

IL-6, CRP and PCT levels in 2 groups

As shown in fig. 2, compared with survivors, non-survivors exhibited significantly higher IL-6, CRP and PCT concentrations (all P < 0.01).

Levels T lymphocyte subsets in 2 groups

The fig. 3 indicated that in contrast to the survival group, the levels of $CD3^+$, $CD3^+CD4^+$ and $CD4^+/CD8^+$ presented reduction, while the level of $CD3^+CD8^+$ presented elevation in the death group (P<0.01).

Prognostic value of LHR, IL-6, CRP, PCT and $CD4^+/CD8^+$ single and combined tests in septic shock patients

ROC curve showed that when LHR, IL-6, CRP, PCT, as well as $CD4^+/CD8^+$ were combined, the AUC for predicting death in septic shock patients was 0.960, better than that of single detection (P<0.05, Fig. 4).

Hemodynamic indexes in 2 groups

Before therapy, no differences were seen in MAP, HR and CVP values between 2 groups (P>0.05). Post-treatment, both groups showed increased MAP and CVP alongside reduced HR, with the observation group demonstrating significantly greater improvements than the control group (P < 0.05) (Fig. 5).

Levels of inflammatory indicators in 2 groups

Prior to treatment, PCT, TNF-α and IL-6 levels were comparable between the two groups (P > 0.05). After therapy, all three markers fell in both groups, with significantly lower values in the observation group than in the control group (P < 0.05) (Fig. 6).

SOFA score in 2 groups

Before therapy, no difference was seen in SOFA score between 2 groups (P>0.05). After therapy, scores fell in both groups, with the observation group showing a significantly greater reduction than the control group (P<0.05) (Fig. 7).

DISCUSSION

The monitoring of septic shock patients includes hemodynamic monitoring and basic monitoring (Esposito *et al*., 2017). The basic monitoring includes capillary filling status, urine volume and blood pressure, etc (Yealy *et al*., 2014). Septic shock often results in a series of clinical manifestations of decreased tissue perfusion, such as decreased urine volume, decreased mean arterial pressure, decreased skin temperature, or decreased capillary refill rate (Guo *et al*., 2024). These signs can be used as observation indicators and diagnostic basis for septic shock (Cecconi *et al*., 2018). Hemodynamic monitoring can understand the status of tissue perfusion and oxygen metabolism, volume resuscitation and circulation, which is particularly important for early diagnosis, treatment and prognosis of septic shock (Lipcsey *et al*., 2015). However, some of the above clinical symptoms are non-specific, which may lead to misdiagnosis and delay the best time for treatment (Cecconi *et al*., 2014). Hence, beyond standardized therapy, reliable prognostic biomarkers are essential to curb septic-shock mortality.

Immune status and the magnitude of the inflammatory response are central to septic-shock pathophysiology and disease progression (Asehnoune *et al*., 2018). When the body goes into septic shock, the level of inflammatory factors increases significantly, causing a series of immune responses and inflammatory reactions, resulting in changes in host cell antigen structure and then causing immune dysfunction (King *et al*., 2014).

Among them, T lymphocyte subsets are one of the most important defense cells in the body against infection (Crausaz *et al*., 2022). Based on surface antigen profiles, T lymphocytes are parsed into CD3+CD4+ helper and CD3+CD8+ cytotoxic subsets (Natalini *et al*., 2021). Under normal circumstances, $CD3^+CD4^+$ and $CD3^+CD8^+$ will feedback and adjust each other to be in a dynamic balance, so the level of $CD4^+/CD8^+$ is commonly used clinically to reflect the abnormal immune function of the body (Pant *et al*., 2014) . In our study, we discovered that in contrast to the survival group, $CD3^+$, $CD3^+CD4^+$ as well as $CD4^+/CD8^+$ levels presented reduction, while the level of $CD3^+CD8^+$ presented elevation in the death group, which was consistent with previous literatures (Monserrat *et al*., 2009, Chen *et al*., 2011).

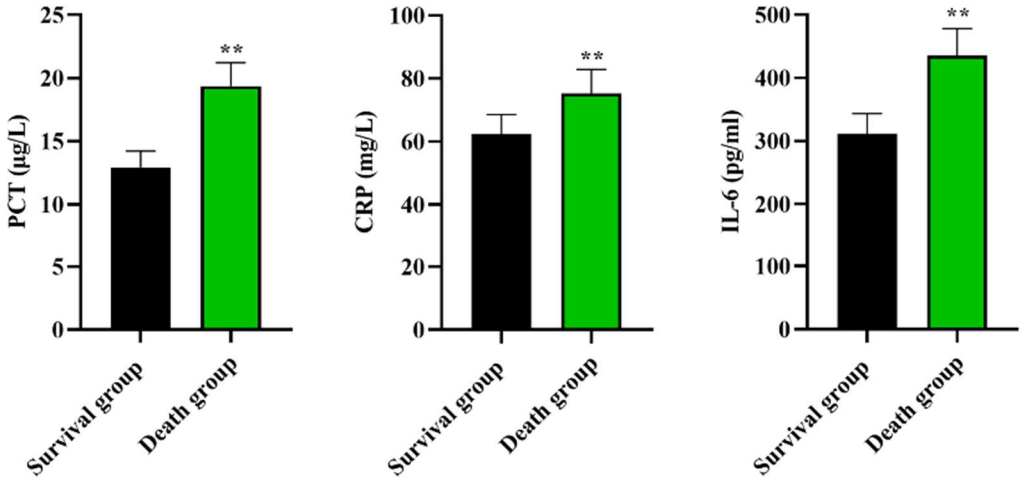

Fig. 2: Levels of IL-6, CRP, PCT in survival and death groups. (a) PCT levels in survival and death groups, (b) CRP levels in survival and death groups and (c) IL-6 levels in survival and death groups.
**P<0.01; IL-6: interleukin 6; CRP: C-reactive protein; PCT: procalcitonin.

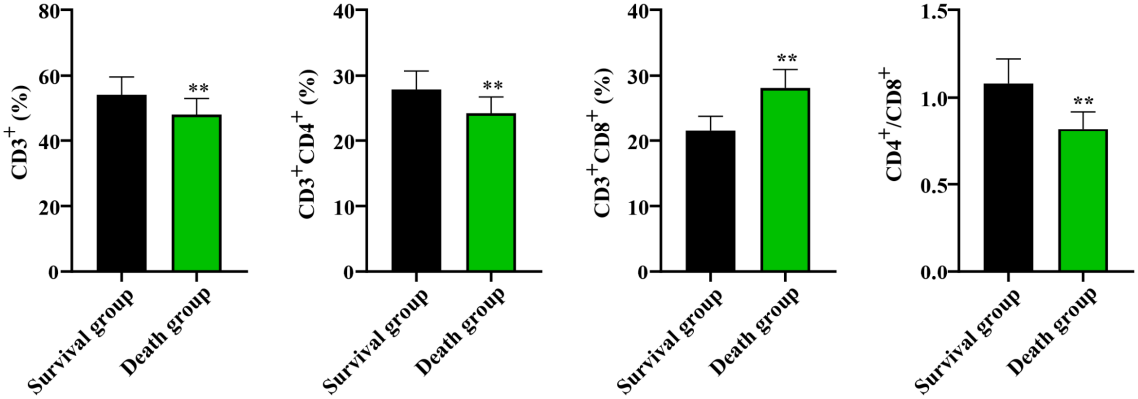

Fig. 3: levels of T lymphocyte subsets in survival and death groups. (a) CD3+ levels in survival and death groups, (b) CD3+CD4+ levels in survival and death groups, (c) CD3+CD8+ levels in survival and death groups and (d) CD4+/CD8+ ratio in survival and death groups. **P<0.01.

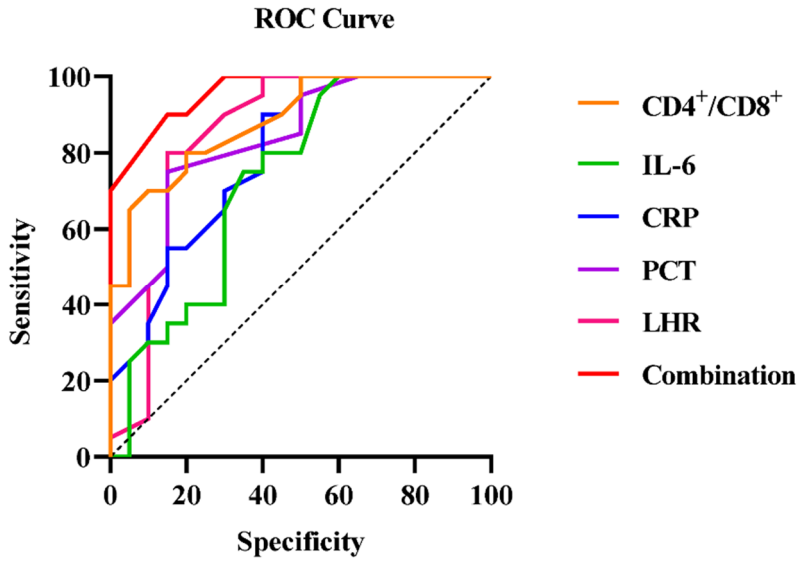

Fig. 4: Prognostic value of LHR, IL-6, CRP, PCT and $CD4^+/CD8^+$ single and combined tests in septic shock patients.
ROC: receiver operating characteristic; LHR: lymphocyte-to-high-density lipoprotein ratio; IL-6: interleukin 6; CRP: C-reactive protein; PCT: procalcitonin.

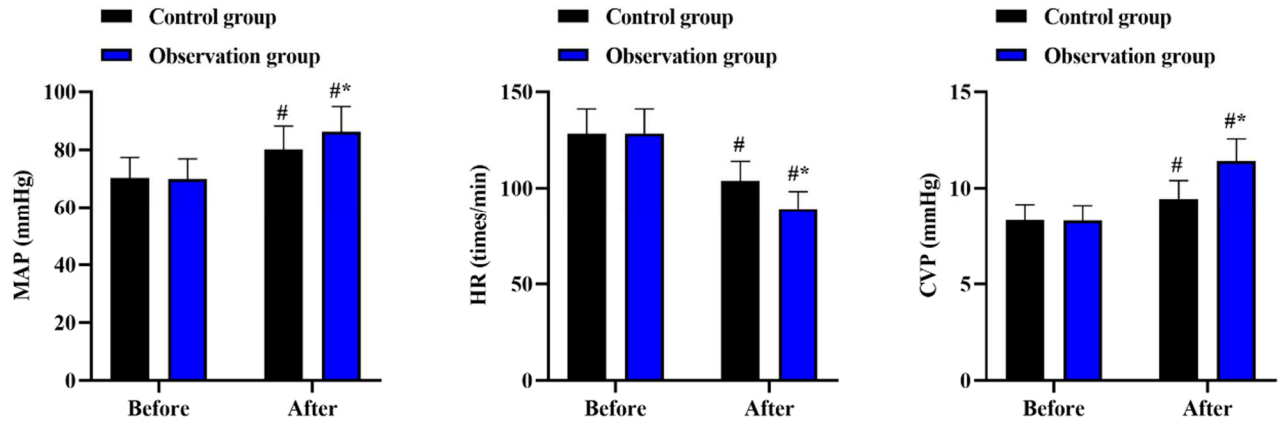

Fig. 5: Hemodynamic indexes in 2 groups. **(a)** MAP levels in control and observation groups, **(b)** HR levels in control and observation groups and **(c)** CVP levels in control and observation groups.
#P<0.05, compared with before therapy; *P<0.05, compared with control group; control group: hydrocortisone; observation: hydrocortisone with vitamin C; MAP: mean arterial pressure; HR: heart rate; CVP: central venous pressure.

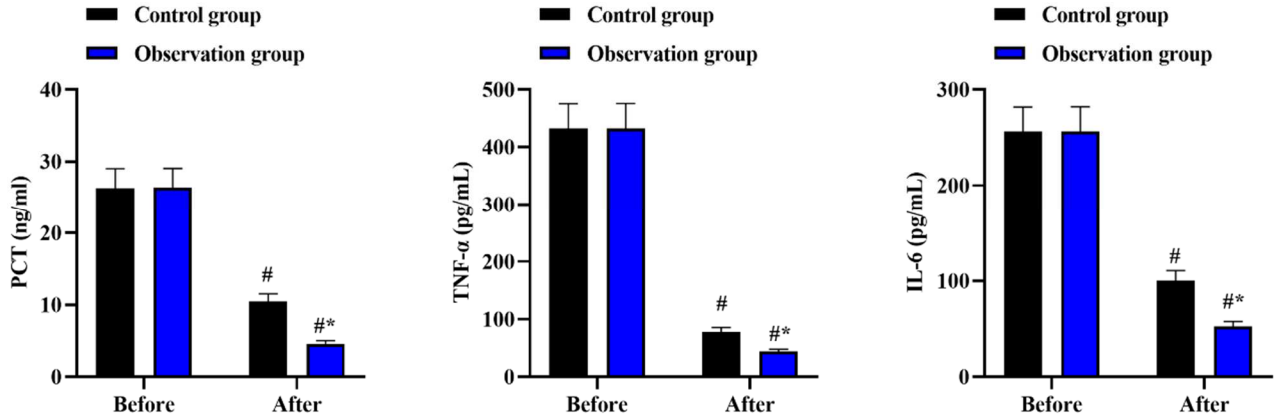

Fig. 6: Levels of inflammatory indicators in 2 groups. **(a)** PCT levels in control and observation groups, **(b)** TNF-α levels in control and observation groups and **(c)** IL-6 levels in control and observation groups.
#P<0.05, compared with before therapy; *P<0.05, compared with control group; control group: hydrocortisone; observation: hydrocortisone with vitamin C; PCT: procalcitonin; TNF-α: tumor necrosis factor-α; IL-6: interleukin 6.

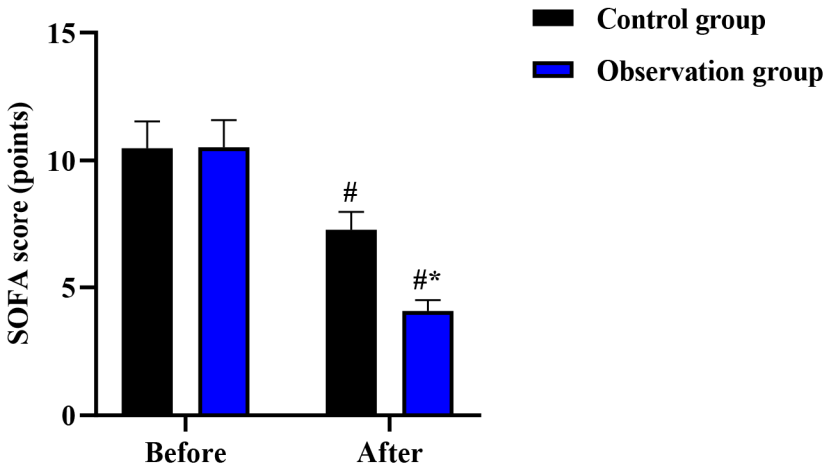

Fig. 7: SOFA score in 2 groups.
#P<0.05, compared with before therapy; *P<0.05, compared with control group; SOFA: Sequential Organ Failure Assessment.

Hepatic-derived CRP is an inflammatory biomarker whose circulating concentration mirrors systemic inflammation (Coventry *et al*., 2009). PCT belongs to a mediator of the body's inflammatory response and the level of expression in the blood of the body will increase once the infection occurs (Li *et al*., 2021). It has been reported that during septic shock, the release of inflammatory factors will increase and the serum PCT level will rise and the rising level is related to the severity of infection (Liang and Yu, 2022). IL-6 is a pro-inflammatory factor with multiple functions secreted mainly by mononuclear macrophages, which plays a central role in inflammatory response and can induce the production of CRP, PCT and other inflammatory factors, which is one of the important indicators reflecting the systemic inflammatory response (Kang *et al*., 2020).

In our study, we discovered that in contrast to the survival group, IL-6, CRP as well as PCT levels presented elevation in the death group. Likewise, Thao *et al*. identified an intensive care unit-admission IL-6 drop ≥86 % within 24 h as a survival indicator in septic shock (Thao *et al*., 2018). Cui *et al*. found serum PCT and CRP to be reliable diagnostic and prognostic indicators in septic shock (Cui *et al*., 2019).

HDL has the functions of regulating immune response, neutralizing endotoxin, anti-oxidation and protecting endothelial cells (Mo *et al*., 2016). HDL is the main source of vitamin E in type II alveolar epithelial cells and the lipoprotein with the highest binding energy with LPS, so it has been widely concerned and studied in septic shock and pulmonary anti-inflammatory reaction (Wang *et al*., 2021). The more severe the condition of septic shock, the more the combination of HDL and LPS leads to the decrease in HDL level (Trinder *et al*., 2021). Therefore, the decrease in HDL levels is linked to poor prognosis of septic shock patients (Prado *et al*., 2023). LHR, a recently introduced inflammatory marker, has demonstrated efficacy in predicting metabolic syndrome severity (Yu *et al*., 2021). Herein, the results indicated that in contrast to the survival group, the level of LHR presented lower in the death group. Consistently, Liu *et al*., indicated that LHR predicts mortality in sepsis patients (Liu *et al*., 2023). In addition, ROC curve showed that when LHR, IL-6, CRP, PCT and $CD4^+/CD8^+$ were combined, the AUC for predicting death in septic shock patients was 0.960, better than that of single detection. These results indicated that all five indices could predict the prognosis of patients and the combination of the three indices could predict the prognosis more accurately, which had important clinical value.

Recent evidence has linked vitamin C to septic shock and prompted its investigation as an adjunctive therapy (Marik *et al*., 2017). There are several possible mechanisms for vitamin C adjuvant treatment of septic shock: (1) Anti-inflammatory effect: Vitamin C can inhibit tumor necrosis factor-α-induced nuclear transcription factor-κB activation by inhibiting the phosphorylation of inhibitory protein-α of nuclear factor-κB, thereby reducing the production of inflammatory mediators and reducing circulating histamine levels (Holford *et al*., 2020). (2) Direct antibacterial activity: High concentration of vitamin C can directly inhibit bacterial growth and show bactericidal activity in vitro (Majtan *et al*., 2020). (3) Antioxidant effect: Vitamin C is the most important antioxidant in the human body and the only one in blood plasma that can protect lipids from peroxidation damage. It reduces inflammation by effectively removing the anti-lipid peroxidation of free radicals (Doseděl *et al*., 2021). (4) Regulate vascular reactivity and improve microcirculatory blood flow: As a coenzyme of dopamine β-hydroxylase, tyrosine hydroxylase and peptidyl glycine α-amide-monooxygenase during the synthesis of norepinephrine and vasopressin, vitamin C can not only increase the endogenous synthesis of norepinephrine and vasopressin, but also enhance the activity of adrenergic receptors and promote the recycling of enzyme cofactor BH4 and these vasoactive substances can improve microcirculation and maintain organ perfusion, thereby improving the body's shock state, reducing the incidence of multiple organ failure and improving the prognosis of septic shock (Biesalski and McGregor, 2007). (5) Immunomodulatory effect: vitamin C can not only enhance the activity of natural killer cells, but also promote the proliferation, differentiation and maturation of immune cells, enhance neutrophil phagocytosis, improve chemotaxis and inhibit multiple organ failure (Juneja *et al*., 2022). (6) Involvement in oxidative stress: Vitamin C is necessary for hypoxia induced factor-1α (HIF-1α) to be hydroxylated by propyl, lysyl hydroxylase and asparaginyl hydroxylase (Kaźmierczak-Barańska *et al*., 2020). HIF-1α is a protein transcription factor that regulates hundreds of genes in response to hypoxia and stress (Li *et al*., 2019) and various pathophysiological mechanisms of septic shock are significantly related to oxidative stress. Therefore, vitamin C supplementation can regulate the oxidative stress response in sepsis patients, thereby delaying the course of the disease and improving the prognosis (Kashiouris *et al*., 2020). (7) Protect endothelial barrier function and enhance innate immunity: Vitamin C is a cofactor of propil 3-hydroxylase, prolyl 4-hydroxylase and lysyl hydroxylase, which can catalyze the biosynthesis of procollagen and elastin, induce collagen gene expression in fibroblasts, stimulate the production of new collagen, promote wound healing, protect skin integrity, enhance endothelial barrier function and enhance innate immunity (Carr and Maggini, 2017).

Following treatment, both groups exhibited higher MAP and CVP and lower HR, yet these improvements were significantly greater in the vitamin C-plus-hydrocortisone arm. Concomitantly, PCT, TNF-α, IL-6 and SOFA scores decreased in both cohorts, with the observation group

showing markedly lower values, indicating enhanced anti-inflammatory effects and better outcomes. These findings corroborate Marik *et al*., who reported that intravenous vitamin C combined with corticosteroids and thiamine attenuates organ dysfunction and reduces mortality in severe sepsis and septic shock. (Marik *et al*., 2017). Liang *et al*. found that vitamin C administration markedly enhances the delta SOFA score in patients with sepsis or septic shock. (Liang *et al*., 2023).

The present investigation has several strengths. First, we combined immunological (T-lymphocyte subsets and LHR), inflammatory (IL-6, CRP, PCT, TNF-α) and classical hemodynamic indices (MAP, CVP, HR), giving a multidimensional picture of septic-shock pathophysiology. Second, the use of ROC-derived AUCs with non-parametric comparison allowed us to demonstrate that the integrated panel markedly outperforms any single marker for 28-day mortality prediction. Nevertheless, several limitations should be acknowledged. The single-center design and the modest sample size limit external validity. We did not perform longitudinal sampling beyond day 7; therefore, the kinetics of immune recovery or rebound inflammation remain unknown. Additionally, vitamin C's mechanisms were not explored at the molecular level (e.g., oxidative stress markers). Future multicenter studies with larger cohorts and mechanistic assays are warranted to confirm these findings.

CONCLUSION

The combination of LHR, IL-6, CRP, PCT and $CD4^+/CD8^+$ has a certain reference value for assessing the severity as well as prognosis of septic shock patients. In clinical practice, the above indices can be combined to make a reasonable judgment of the patient's condition and guide clinical treatment. In addition, our study indicates that vitamin C can improve hemodynamic indexes, inflammatory response and prognosis of septic shock patients.

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Authors' contributions
Yuyu Lu: Writing original draft; Ling Wu: Review & editing the manuscript; Lingling Nie: Design and revise the manuscript.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
The ethical approval was obtained from the Affiliated Jiangning Hospital of Nanjing Medical University, with the ethical number 2022-03-048-K01.

Conflict of interest
The authors declare no competing financial or personal interests.

REFERENCES

Asehnoune K, Roquilly A and Vourc'h M (2018). Monitoring the adaptive immune system in septic shock patients: Ready for prime time? *Crit. Care Med.,* **46**(11): 1867-1869.

Biesalski HK and McGregor GP (2007). Antioxidant therapy in critical care--is the microcirculation the primary target? *Crit. Care Med.,* **35**(9 Suppl): S577-583.

Böttger F, Vallés-Martí A, Cahn L and Jimenez CR (2021). High-dose intravenous vitamin C, a promising multi-targeting agent in the treatment of cancer. *J. Exp. Clin. Cancer Res.,* **40**(1): 343.

Carr AC and Maggini S (2017). Vitamin C and immune function. *Nutrients,* **9**(11): 1211.

Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL and Rhodes A (2014). Consensus on circulatory shock and hemodynamic monitoring. task force of the european society of intensive care medicine. *Intensive Care Med.,* **40**(12): 1795-1815.

Cecconi M, Evans L, Levy M and Rhodes A (2018). Sepsis and septic shock. *Lancet,* **392**(10141): 75-87.

Chen H, Xiong C, Shao X, Ning J, Gao P, Xiao H, Chen Y, Zou Z, Hong G, Li X, Shao M, Sheng J, Yang X, You X and Zou H (2019). Lymphocyte to high-density lipoprotein ratio as a new indicator of inflammation and metabolic syndrome. *Diabetes Metab Syndr. Obes.,* **12**: 2117-2123.

Chen X, Ye J and Ye J (2011). Analysis of peripheral blood lymphocyte subsets and prognosis in patients with septic shock. *Microbiol. Immunol.,* **55**(10) 736-742.

Coventry BJ, Ashdown ML, Quinn MA, Markovic SN, Yatomi-Clarke SL and Robinson AP (2009). CRP identifies homeostatic immune oscillations in cancer patients: A potential treatment targeting tool? *J. Transl. Med.,* **7**: 102.

Crausaz M, Monneret G, Conti F, Lukaszewicz AC, Marchand JB, Martin P, Inchauspe G and Venet F (2022). A novel virotherapy encoding human interleukin-7 improves ex vivo T lymphocyte functions in immunosuppressed patients with septic shock and critically ill COVID-19. *Front. Immunol.,* **13**: 939899.

Cui N, Zhang H, Chen Z and Yu Z (2019). Prognostic significance of PCT and CRP evaluation for adult ICU patients with sepsis and septic shock: Retrospective analysis of 59 cases. *J. Int. Med. Res.,* **47**(4): 1573-1579.

Dosedel M, Jirkovsky E, Macakova K, Krcmova LK,

Javorska L, Pourova J, Mercolini L, Remiao F, Novakova L, Mladanka P and On Behalf Of The O (2021). Vitamin C-sources, physiological role, kinetics, Deficiency, use, toxicity and determination. *Nutrients,* **13**(2): 615.

Esposito S, De Simone G, Boccia G, De Caro F and Pagliano P (2017). Sepsis and septic shock: New definitions, new diagnostic and therapeutic approaches. *J. Glob. Antimicrob. Resist.,* **10**: 204-212.

Ford JS, Morrison JC, Kyaw M, Hewlett M, Tahir P, Jain S, Nemati S, Malhotra A and Wardi G (2025). The effect of severe sepsis and septic shock management bundle (SEP-1) compliance and implementation on mortality among patients with sepsis: A systematic review. *Ann. Intern. Med.,* **178**(4): 543-557.

Foster DM. Kellum JA (2023). Endotoxic septic shock: Diagnosis and treatment. *Int. J. Mol. Sci.,* **24**(22): 16185.

Fujii T, Salanti G, Belletti A, Bellomo R, Carr A, Furukawa TA, Luethi N, Luo Y, Putzu A, Sartini C, Tsujimoto Y, Udy AA, Yanase F and Young PJ (2022). Effect of adjunctive vitamin C, glucocorticoids and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: A systematic review and a component network meta-analysis. *Intensive Care Med.,* **48**(1): 16-24.

García-de-Acilu M, Mesquida J, Gruartmoner G and Ferrer R (2021). Hemodynamic support in septic shock. *Curr. Opin. Anaesthesiol.,* **34**(2): 99-106.

Gu X, Zhou F, Wang Y, Fan G and Cao B (2020). Respiratory viral sepsis: Epidemiology, pathophysiology, diagnosis and treatment. *Eur. Respir. Rev.,* **29**(157): 200038.

Gu Y, Tang J, Zhang F, Qu Y, Zhao M, Li M, Xie Z, Wang X, Song L, Jiang Z, Wang Y, Shen X and Xu L (2023). Manganese potentiates lipopolysaccharide-induced innate immune responses and septic shock. *Int. J. Biol. Macromol.,* **230**:123202.

Guo Q, Liu D, Wang X and Chinese Critical Ultrasound Study Group (2024). Early peripheral perfusion monitoring in septic shock. *Eur J Med Res.,* **29**(1): 477.

Hagel S, Bach F, Brenner T, Bracht H, Brinkmann A, Annecke T, Hohn A, Weigand M, Michels G, Kluge S, Nierhaus A, Jarczak D, König C, Weismann D, Frey O, Witzke D, Muller C, Bauer M, Kiehntopf M, Neugebauer S, Lehmann T, Roberts JA and Pletz MW (2022). Effect of therapeutic drug monitoring-based dose optimization of piperacillin/tazobactam on sepsis-related organ dysfunction in patients with sepsis: A randomized controlled trial. *Intensive Care Med.,* **48**(3): 311-321.

Han YH, Onufer EJ, Huang LH, Sprung RW, Davidson WS, Czepielewski RS, Wohltmann M, Sorci-Thomas MG, Warner BW and Randolph GJ (2021). Enterically derived high-density lipoprotein restrains liver injury through the portal vein. *Science,* **373**(6553): eabe6729.

Hernández G, Ospina-Tascon GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, Friedman G, Castro R, Alegría L, Teboul JL, Cecconi M, Ferri G, Jibaja M, Pairumani R, Fernández P, Barahona D, Granda-Luna V, Cavalcanti AB, Bakker J, Hernández G, Ospina-Tascón G, Petri Damiani L, Estenssoro E, Dubin A, Hurtado J, Friedman G, Castro R, Alegría L, Teboul JL, Cecconi M, Cecconi M, Ferri G, Jibaja M, Pairumani R, Fernández P, Barahona D, Cavalcanti AB, Bakker J, Hernández G, Alegría L, Ferri G, Rodriguez N, Holger P, Soto N, Pozo M, Bakker J, Cook D, Vincent JL, Rhodes A, Kavanagh BP, Dellinger P, Rietdijk W, Carpio D, Pavéz N, Henriquez E, Bravo S, Valenzuela ED, Vera M, Dreyse J, Oviedo V, Cid MA, Larroulet M, Petruska E, Sarabia C, Gallardo D, Sanchez JE, González H, Arancibia JM, Muñoz A, Ramirez G, Aravena F, Aquevedo A, Zambrano F, Bozinovic M, Valle F, Ramirez M, Rossel V, Muñoz P, Ceballos C, Esveile C, Carmona C, Candia E, Mendoza D, Sanchez A, Ponce D, Ponce D, Lastra J, Nahuelpán B, Fasce F, Luengo C, Medel N, Cortés C, Campassi L, Rubatto P, Horna N, Furche M, Pendino JC, Bettini L, Lovesio C, González MC, Rodruguez J, Canales H, Caminos F, Galletti C, Minoldo E, Aramburu MJ, Olmos D, Nin N, Tenzi J, Quiroga C, Lacuesta P, Gaudín A, Pais R, Silvestre A, Olivera G, Rieppi G, Berrutti D, Ochoa M, Cobos P, Vintimilla F, Ramirez V, Tobar M, García F, Picoita F, Remache N, Granda V, Paredes F, Barzallo E, Garcés P, Guerrero F, Salazar S, Torres G, Tana C, Calahorrano J, Solis F, Torres P, Herrera L, Ornes A, Peréz V, Delgado G, López A, Espinosa E, Moreira J, Salcedo B, Villacres I, Suing J, Lopez M, Gomez L, Toctaquiza G, Cadena Zapata M, Orazabal MA, Pardo Espejo R, Jimenez J, Calderón A, Paredes G, Barberán JL, Moya T, Atehortua H, Sabogal R, Ortiz G, Lara A, Sanchez F, Hernán Portilla A, Dávila H, Mora JA, Calderón LE, Alvarez I, Escobar E, Bejarano A, Bustamante LA and Aldana JL (2019). Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-Day mortality among patients with septic shock: The andromeda-shock randomized clinical trial. *JAMA,* **321**(7): 654-664.

Holford P, Carr AC, Jovic TH, Ali SR, Whitaker IS, Marik PE and Smith AD (2020). Vitamin C-An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19. *Nutrients,* **12**(12): 3760.

Juneja D, Nasa P and Jain R (2022). Current role of high dose vitamin C in sepsis management: A concise review. *World J. Crit. Care Med.,* **11**(6): 349-363.

Kang S, Narazaki M, Metwally H and Kishimoto T (2020). Historical overview of the interleukin-6 family cytokine. *J. Exp. Med.,* **217**(5): e20190347.

Kashiouris MG, L'Heureux M, Cable CA, Fisher BJ, Leichtle SW and Fowler AA (2020). The Emerging Role of Vitamin C as a Treatment for Sepsis. *Nutrients,* **12**(2): 292.

Kaźmierczak-Barańska J, Boguszewska K, Adamus-Grabicka A. Karwowski BT (2020). Two Faces of Vitamin C-Antioxidative and Pro-Oxidative Agent. *Nutrients,* **12**(5): 1501.

King EG, Bauzá GJ, Mella JR. Remick DG (2014). Pathophysiologic mechanisms in septic shock. *Lab Invest.,* **94**(1): 4-12.

Li HS, Zhou YN, Li L, Li SF, Long D, Chen XL, Zhang JB, Feng L. Li YP (2019). HIF-1α protects against oxidative stress by directly targeting mitochondria. *Redox Biol.,* **25**: 101109.

Li X, Huang C, Rai KR. Xu Q (2025). Innate immune role of IL-6 in influenza a virus pathogenesis. *Front Cell Infect Microbiol.,* **15**: 1605446.

Li Y, Min L. Zhang X (2021). Usefulness of procalcitonin (PCT), C-reactive protein (CRP) and white blood cell (WBC) levels in the differential diagnosis of acute bacterial, viral and mycoplasmal respiratory tract infections in children. *BMC Pulm Med.,* **21**(1): 386.

Liang B, Su J, Shao H, Chen H and Xie B (2023). The outcome of IV vitamin C therapy in patients with sepsis or septic shock: a meta-analysis of randomized controlled trials. *Crit Care,* **27**(1): 109.

Liang P. Yu F (2022). Predictive value of procalcitonin and neutrophil-to-lymphocyte ratio variations for bloodstream infection with septic shock. *Med. Sci. Monit.,* **28**: e935966.

Lipcsey M, Castegren M and Bellomo R (2015). Hemodynamic management of septic shock. *Minerva Anestesiol.,* **81**(11): 1262-1272.

Liu W, Tao Q, Xiao J, Du Y, Pan T, Wang Y and Zhong X (2023). Low lymphocyte to high-density lipoprotein ratio predicts mortality in sepsis patients. *Front. Immunol.,* **14**: 1279291.

Majtan J, Sojka M, Palenikova H, Bucekova M and Majtan V (2020). Vitamin C enhances the antibacterial activity of honey against planktonic and biofilm-embedded Bacteria. *Molecules,* **25**(4): 992.

Marik PE (2018). Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol Ther.,* **189**: 63-70.

Marik PE, Khangoora V, Rivera R, Hooper MH and Catravas J (2017). Hydrocortisone, vitamin C and thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest,* **151**(6): 1229-1238.

Mo ZC, Ren K, Liu X, Tang ZL and Yi GH (2016). A high-density lipoprotein-mediated drug delivery system. *Adv. Drug Deliv. Rev.,* **106**(Pt A): 132-147.

Monserrat J, de Pablo R, Reyes E, Díaz D, Barcenilla H, Zapata MR, De la Hera A, Prieto A and Alvarez-Mon M (2009). Clinical relevance of the severe abnormalities of the T cell compartment in septic shock patients. *Crit. Care,* **13**(1): R26.

Mouillaux J, Allam C, Gossez M, Uberti T, Delwarde B, Hayman J, Rimmelé T, Textoris J, Monneret G, Peronnet E and Venet F (2019). TCR activation mimics CD127(low)PD-1(high) phenotype and functional alterations of T lymphocytes from septic shock patients. *Crit. Care,* **23**(1): 131.

Natalini A, Simonetti S, Favaretto G, Peruzzi G, Antonangeli F, Santoni A, Muñoz-Ruiz M, Hayday A and Di Rosa F (2021). OMIP-079: Cell cycle of CD4(+) and CD8(+) naïve/memory T cell subsets and of Treg cells from mouse spleen. *Cytometry A.,* **99**(12): 1171-1175.

Pant H, Hughes A, Schembri M, Miljkovic D and Krumbiegel D (2014). CD4(+) and CD8(+) regulatory T cells in chronic rhinosinusitis mucosa. *Am. J. Rhinol. Allergy,* **28**(2): e83-89.

Prado Y, Tapia P, Eltit F, Reyes-Martínez C, Feijóo CG, Llancalahuen FM, Riedel CA, Cabello-Verrugio C, Stehberg J and Simon F (2023). Sepsis-induced coagulopathy phenotype induced by oxidized high-density lipoprotein associated with increased mortality in septic-shock patients. *Antioxidants (Basel),* **12**(3).

Puthucheary Z, Tadié JM and Patel JJ (2022). C-reactive protein in immunometabolism: Spared from 'paying the piper'. *Intensive Care Med.,* **48**(1): 103-105.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL and Angus DC (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA,* **315**(8): 801-810.

Song J, Park DW, Moon S, Cho HJ, Park JH, Seok H and Choi WS (2019). Diagnostic and prognostic value of interleukin-6, pentraxin 3 and procalcitonin levels among sepsis and septic shock patients: A prospective controlled study according to the sepsis-3 definitions. *BMC Infect Dis.,* **19**(1): 968.

Srzić I, Nesek Adam V and Tunjić Pejak D (2022). Sepsis definition: What's new in the treatment guidelines. *Acta. Clin. Croat.,* **61**(Suppl 1): 67-72.

Tanaka S, Diallo D, Delbosc S, Genève C, Zappella N, Yong-Sang J, Patche J, Harrois A, Hamada S, Denamur E, Montravers P, Duranteau J and Meilhac O (2019). High-density lipoprotein (HDL) particle size and concentration changes in septic shock patients. *Ann. Intensive Care,* **9**(1): 68.

Thao PTN, Tra TT, Son NT and Wada K (2018). Reduction in the IL-6 level at 24 h after admission to the intensive care unit is a survival predictor for Vietnamese patients with sepsis and septic shock: A prospective study. *BMC Emerg. Med.,* **18**(1): 39.

Trinder M, Wang Y, Madsen CM, Ponomarev T, Bohunek L, Daisely BA, Julia Kong H, Blauw LL, Nordestgaard BG, Tybjærg-Hansen A, Wurfel MM, Russell JA, Walley KR, Rensen PCN, Boyd JH and Brunham LR (2021). Inhibition of cholesteryl ester transfer protein preserves high-density lipoprotein cholesterol and improves survival in sepsis. *Circulation,* **143**(9): 921-934.

Wang G, Deng J, Li J, Wu C, Dong H, Wu S and Zhong Y (2021). The role of high-density lipoprotein in COVID-19. *Front. Pharmacol.,* **12**: 720283.

Wussler D, Kozhuharov N, Tavares Oliveira M, Bossa A, Sabti Z, Nowak A, Murray K, du Fay de Lavallaz J,

Badertscher P, Twerenbold R, Shrestha S, Flores D, Nestelberger T, Walter J, Boeddinghaus J, Zimmermann T, Koechlin L, von Eckardstein A, Breidthardt T and Mueller C (2019). Clinical utility of procalcitonin in the diagnosis of pneumonia. *Clin. Chem.,* **65**(12): 1532-1542.

Xie J, Wang H, Kang Y, Zhou L, Liu Z, Qin B, Ma X, Cao X, Chen D, Lu W, Yao C, Yu K, Yao X, Shang H, Qiu H. Yang Y (2020). The epidemiology of sepsis in Chinese ICUs: A national cross-sectional survey. *Crit. Care Med.,* **48**(3): e209-e218.

Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI and Angus DC (2014). A randomized trial of protocol-based care for early septic shock. *N. Engl. J. Med.,* **370**(18): 1683-1693.

Yu S, Guo X, Li G, Yang H, Zheng L and Sun Y (2021). Lymphocyte to high-density lipoprotein ratio but not platelet to lymphocyte ratio effectively predicts metabolic syndrome among subjects from rural China. *Front. Cardiovasc. Med.,* **8**: 583320.