Prognostic value of PaO$_2$/FiO$_2$, SOFA and D-dimer in elderly patients with sepsis

Tao Li[1],*, Wan-Qin Hu[2],* iD, Xian Li[2],
Jia-Peng Zhang[2], Li-Zhi Tan[3], Li-Xia Yu[2],
Hai-Rong Gu[2] and Ze-Ya Shi[4]

Abstract

Objective: To investigate the prognostic value for predicting mortality of partial pressure of oxygen/fraction of inspired oxygen (PaO$_2$/FiO$_2$), the Sequential Organ Failure Assessment (SOFA) score and D-dimer in elderly patients with sepsis.

Methods: This retrospective cohort study enrolled elderly patients with sepsis admitted to the intensive care unit (ICU) between January 2019 and October 2020. Patients were divided into a survival group and a non-survival group. Biomarkers, SOFA, Acute Physiology and Chronic Health Evaluation II and Glasgow Coma Scale scores were recorded within 24 h after admission to the ICU.

Results: A total of 135 elderly patients with sepsis were enrolled in the study: 89 were in the survival group and 46 were in the non-survival group at 28 days. Univariate and multivariate regression analyses demonstrated that PaO$_2$/FiO$_2$, SOFA and D-dimer were independently associated with 28-day mortality. The predictive performance for mortality of the combination of PaO$_2$/FiO$_2$, SOFA score and D-dimer (area under the receiver operating characteristic curve of 0.926) was higher than the values for the individual factors (0.761, 0.745 and 0.878, respectively).

Conclusion: The combination of PaO$_2$/FiO$_2$, SOFA score and D-dimer represents a promising tool and biomarker for predicting 28-day mortality of the elderly patients with sepsis.

[4]Department of Nursing, Hunan Provincial People's Hospital, Changsha, Hunan Province, China

*These authors contributed equally to this work.

Corresponding author:
Hai-Rong Gu, Department of Nursing, Jiaying University, 146 Huangtang Road, Meizhou, 514015, Guangdong Province, China.
Email: mzghr@126.com

[1]Department of pathophysiology, Jiaying University, Meizhou, Guangdong Province, China
[2]Department of Nursing, Jiaying University, Meizhou, Guangdong Province, China
[3]Department of Nursing, The Second Xiangya Hospital of Central South University, Changsha, Hunan Province, China

Introduction

According to population statistics for China, the number of people aged ≥ 65 years has increased rapidly in China; with 164.5 million people aged ≥ 65 years and 26 million aged ≥ 80 years.[1,2] It is estimated that by 2050 over 365 million people will be aged ≥ 65 years and they will account for 26.1% of China's total population.[3,4] As the ageing population continues to grow, more elderly patients will be admitted to the intensive care unit (ICU).[5]

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[6] The mean mortality rate of sepsis is 33.2%.[6] In elderly patients with sepsis, the mortality rate is much higher.[7] The incidence and mortality rate of elderly patients with sepsis is increasing as the ageing population continues to increase globally. A previous study demonstrated that increased age was an independent predictor of death among sepsis patients, especially in those aged ≥ 65 years.[8] Diagnosing elderly patients with sepsis is difficult because since they present with few specific signs and symptoms.[9] This poses a challenge for ICU physicians to identify elderly patients with sepsis, especially those at a higher risk of death. The ability to diagnose and predict the clinical symptoms and prognostic outcomes in elderly patients with sepsis is vitally important.

Prognostic indices such as the Sequential Organ Failure Assessment (SOFA) and the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) can be used to predict the outcome of the patients with sepsis,[10,11] but there is little evidence about their value in elderly patients with sepsis. In addition, biological markers such as procalcitonin (PCT), C-reactive protein (CRP), brain natriuretic peptide precursor, lactate (LAC) and D-dimer have been widely used to predict which patients with sepsis are likely to survive.[12,13] However, none of these biological markers have a 100% sensitivity or 100% specificity.

The present study compared different prognostic indices and biomarkers in relation to predicting mortality in elderly patients with sepsis admitted to the ICU.

Patients and methods

Patient population

This single-centre retrospective study enrolled consecutive elderly patients with sepsis admitted to the ICU of Hunan Provincial People's Hospital, Changsha, Hunan Province, China between January 2019 and October 2020. This is a tertiary referral hospital located in the south-central region of China. Elderly patients that were >65 years and diagnosed with sepsis according to SEPSI-3 criteria were recruited.[6] Patients were excluded if they had an end-stage disease such as end-stage renal disease,[14] malignant tumour, liver disease, severe immunodeficiency disease, haematological disease or survived <12 h.

The Medical Ethics Committee of Hunan Provincial People's Hospital approved the study (no. 2021-37). Informed consent was waived due to the retrospective nature of this

study. All patient data were de-identified. The reporting of this study conforms with STROBE guidelines.[15]

Data collection

The demographic characteristics of the patients were collected and documented at the time of admission to the ICU department. Infection sites (respiratory tract, gastrointestinal tract, genitourinary tract and others), vital signs (heart rate, breath rates, blood pressure), comorbidities and the 'do not resuscitate' status were also collected. SOFA, APACHE II and Glasgow Coma Scale (GCS) scores on admission for all enrolled patients were calculated. PCT, white blood cells (WBC), neutrophils (N), CRP, prothrombin time (PT), D-dimer, fibrinogen degradation product (FDP), N-terminal brain natriuretic pro-peptide (NT-proBNP), cardiac troponin I (CTnI), creatine kinase (CK), creatine kinase-MB (CK-MB), LAC, platelets (PLT), bilirubin and creatinine were documented from the patient files. All enrolled patients were followed for up to 28 days through their medical records and the 28-day mortality was the clinical endpoint. According to their outcome at 28 days from admission, patients were divided into non-survival and survival groups.

Serum collection

All blood samples were collected within 24 h of admission to the ICU. These samples were used to measure the following using routine laboratory methods: PCT, WBC, N, CRP, PT, D-dimer, FDP, NT-proBNP, CTnI, CK, CK-MB, LAC, PLT, bilirubin and creatinine.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Comparisons between the non-survival and survival groups were undertaken using Student's t-test for continuous variables and χ^2-test for categorical variables. Multivariate logistic regression analysis was used to determine the risk factors for 28-day mortality in elderly patients with sepsis. Receiver operating characteristic (ROC) curve analysis was used to compare the prognostic value of partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2), SOFA and D-dimer in elderly patients with sepsis. Using the area under the curve (AUC) to assess their predictive values. A P-value <0.05 was considered statistically significant.

Results

A total of 135 patients were enrolled in this retrospective study. After a follow-up of 28 days, 89 patients had survived and 46 patients had died (Table 1). No significant differences in age, sex, infection sites, comorbidities, 'do not resuscitate' status, heart rate, systolic blood pressure, diastolic blood pressure, platelet count, bilirubin, central venous pressure and creatinine were found between the non-survival and survival groups. The respiration rate was significantly higher in the non-survival group compared with the survival group ($P = 0.039$). SOFA and APACHE II scores in the non-survival group were significantly higher than in the survival group ($P < 0.001$ for all comparisons). The PaO_2/FiO_2 and GCS scores was significantly lower in the non-survival group compared with the survival group ($P < 0.001$ for both comparisons). PT, D-dimer and LAC were significantly higher in the non-survival group compared with the survival group ($P < 0.05$ for all comparisons). There were no significant differences between the non-survival and survival groups in terms of PCT, WBC, N, CRP, FDP, NT-proBNP, CTnI, CK and CK-MB.

Table 1. Clinical, demographic and biomarker data for elderly patients with sepsis ($n = 135$) enrolled in a study that compared different prognostic indices and biomarkers in relation to predicting mortality in elderly patients with sepsis admitted to the intensive care unit.

Characteristic	Survival group $n = 89$	Non-survival group $n = 46$	t/χ^2	Statistical analysis[a]
Demographics				
Age, years	65.38 ± 5.67	67.33 ± 8.49	-1.584	NS
Sex				
Male	45 (51%)	27 (59%)	0.801	NS
Female	44 (49%)	19 (41%)		
Infection site				
Respiratory tract	54	28	1.334	NS
Gastrointestinal tract	20	8		
Genitourinary tract	10	8		
Others	5	2		
Comorbidities				
Chronic respiratory disease	23	15	0.887	NS
Chronic cardiovascular disease	18	7		
Diabetes mellitus	34	18		
Chronic neurological disease	16	9		
Do not resuscitate status	12	7	0.075	NS
Vital signs				
Heart rate, beats/min	99.67 ± 18.65	106.13 ± 27.02	-1.452	NS
Systolic pressure, mmHg	114.78 ± 22.93	122.80 ± 33.77	-1.623	NS
Diastolic pressure, mmHg	69.86 ± 16.07	71.44 ± 16.13	-0.537	NS
Respiration rate, breaths/min	23.64 ± 8.72	26.59 ± 5.58	-2.080	$P = 0.039$
SOFA factors				
PaO_2/FiO_2	195.06 ± 39.92	109.69 ± 28.38	5.352	$P < 0.001$
Platelets, $\times 10^9/l$	180.87 ± 96.43	153.82 ± 108.95	1.477	NS
Bilirubin, $\mu mol/l$	21.75 ± 29.17	30.62 ± 50.64	-1.096	NS
CVP, mmHg	85.42 ± 16.78	87.79 ± 20.89	-0.700	NS
GCS score	14.96 ± 0.26	13.87 ± 1.94	3.779	$P < 0.001$
Creatinine, $\mu mol/l$	157.08 ± 242.48	188.70 ± 231.51	-0.729	NS
SOFA score	3.29 ± 1.13	6.14 ± 2.36	-6.134	$P < 0.001$
APACHE II score	8.55 ± 4.97	15.21 ± 6.21	-6.773	$P < 0.001$
Laboratory results				
PCT, ng/ml	11.72 ± 25.95	21.07 ± 31.72	-1.708	NS
WBC, $\times 10^9/l$	14.38 ± 8.75	12.90 ± 7.42	0.984	NS
N, $\times 10/l$	82.05 ± 17.94	83.95 ± 17.49	-0.588	NS
CRP, mg/l	110.06 ± 73.46	121.12 ± 101.73	-0.722	NS
PT, s	15.69 ± 5.39	18.45 ± 6.54	-2.503	$P = 0.014$
D-dimer, mg/l	3.21 ± 1.66	6.86 ± 2.80	-8.129	$P < 0.001$
FDP, ng/l	17.84 ± 6.72	18.14 ± 4.39	-0.297	NS
NT-proBNP, fmol/ml	2.94 ± 0.71	3.11 ± 0.57	-1.455	NS
CTnI, $\mu g/l$	1.45 ± 0.56	1.56 ± 0.64	-1.001	NS
CK, U/l	167.65 ± 49.70	170.26 ± 45.00	-0.299	NS

(continued)

Table 1. Continued.

Characteristic	Survival group $n = 89$	Non-survival group $n = 46$	t/χ^2	Statistical analysis[a]
CK-MB, U/l	26.02 ± 5.88	27.06 ± 5.44	−0.977	NS
LAC, mmol/l	1.85 ± 0.829	2.21 ± 0.741	−2.488	$P = 0.014$

Data presented as mean ± SD or *n* of patients (%).

[a]Comparisons between the non-survival and survival groups were undertaken using Student's *t*-test for continuous variables and χ^2-test for categorical variables.

SOFA, Sequential Organ Failure Assessment; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; CVP, central venous pressure; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; PCT, procalcitonin; WBC, white blood cells; N, neutrophils; CRP, C-reactive protein; PT, prothrombin time; FDP, fibrinogen degradation product; NT-proBNP, N-terminal brain natriuretic propeptide; CTnI, cardiac troponin I; CK, creatine kinase; CK-MB, creatine kinase-MB; LAC, lactate; NS, no significant between-group difference ($P \geq 0.05$).

Table 2. Multivariate logistic regression analysis of risk factors for 28-day mortality in elderly patients with sepsis ($n = 135$).

Factor	β	SE	Wald χ^2	OR	95% CI	*P*-value
Respiration rate	−0.003	0.768	0.000	0.997	0.221, 4.491	NS
PaO_2/FiO_2	1.242	0.584	4.518	3.461	1.102, 10.873	$P = 0.034$
SOFA score	0.450	0.090	25.091	1.568	1.315, 1.869	$P < 0.001$
GCS score	1.052	1.196	0.773	2.863	0.275, 29.840	NS
APACHE II score	0.225	0.047	23.151	1.253	1.143, 1.373	$P < 0.001$
PT	0.969	0.784	1.526	2.635	0.566, 12.261	NS
D-dimer	0.647	0.170	14.396	1.909	1.367, 2.666	$P < 0.001$
LAC	0.434	0.606	0.512	1.543	0.471, 5.058	NS
Constant	−33.199	20710.190	0.000	0.999		$P < 0.001$

SE, standard error; OR, odds ratio; CI, confidence interval; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; PT, prothrombin time; LAC, lactate; NS, no significant association ($P \geq 0.05$).

As shown in Table 2, multivariate logistic regression analysis showed that PaO_2/FiO_2, SOFA and D-dimer were risk factors for the 28-day mortality of elderly patients with sepsis.

Receiver operating characteristic curves were used to evaluate the prognostic value of the three factors in elderly patients with sepsis (Figure 1). The results showed that the AUCs of PaO_2/FiO_2, SOFA and D-dimer were 0.761 (95% confidence interval [CI], 0.669, 0.853), 0.745 (95% CI, 0.663, 0.827) and 0.878 (95% CI, 0.822, 0.934), respectively (Table 3). The sensitivity and specificity of the cut-off values were calculated according to ROC curve analysis. The prognostic value of the combined PaO_2/FiO_2, SOFA and D-dimer levels in elderly patients with sepsis was higher than the values for the individual factors ($P < 0.001$).

Discussion

Sepsis has become one of the main causes of death in the geriatric population.[16] Elderly patients with sepsis account for 58–65% of
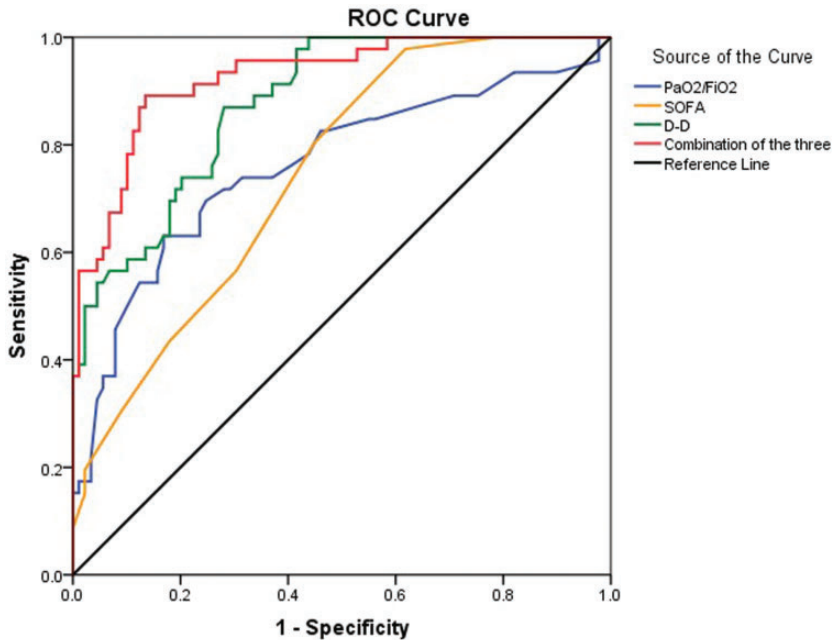
Figure 1. Receiver operating characteristic (ROC) curve analysis of the prognostic value of partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2), the Sequential Organ Failure Assessment (SOFA) score and D-dimer for 28-day mortality of elderly patients with sepsis ($n = 135$). The colour version of this figure is available at: http://imr.sagepub.com.

Table 3. Receiver operating characteristic curve (ROC) analysis of the prognostic value of partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2), the Sequential Organ Failure Assessment (SOFA) score and D-dimer for 28-day mortality of elderly patients with sepsis ($n = 135$).

Factor	Area under the ROC	Sensitivity	Specificity	Cut-off	95% CI	P-value
PaO_2/FiO_2	0.761	63.0%	83.1%	227.27	0.669, 0.853	$P < 0.001$
SOFA	0.745	97.8%	38.2%	1.5	0.663, 0.827	$P = 0.004$
D-Dimer	0.878	87.0%	71.9%	4.16	0.822, 0.934	$P < 0.001$
PaO_2/FiO_2 & SOFA & D-dimer	0.926	0.89.1%	86.5%	–	0.881, 0.971	$P < 0.001$

all patients with sepsis.[17–19] Studies have shown that the incidence and mortality of sepsis increase with age.[20,21] For example, the mortality rate of sepsis in children is 10%, but it is 26% in those aged 60–64 years and 38% in patients aged ≥85 years.[20,21] Previous studies have shown that most elderly patients with sepsis are prone to acute renal failure, respiratory failure and multiple organ dysfunction syndrome (MODS) because of the deterioration in their physical function and poor organ compensatory function.[22] Compared with adult patients, elderly patients have fewer signs and symptoms of infection and more easily develop septic shock.[9] Therefore, the early detection and prognostic evaluation would be more meaningful in this population.

The present study evaluated the values of biological markers and prognostic indices in predicting mortality in elderly patients with sepsis. The results showed that PaO_2/FiO_2, SOFA and D-dimer in the non-survival group were significantly higher compared with the survival group. The prognostic value of the combined PaO_2/FiO_2, SOFA and D-dimer levels in elderly patients with sepsis was higher than the values for the individual factors.

The SOFA score is a better tool for predicting in-hospital mortality than quick SOFA, Systemic Inflammatory Response Syndrome and APACHE II scores.[23,24] A previous study demonstrated that the SOFA score can be used as a tool to predict the outcomes of patients with sepsis and it had the strongest association with 28-day mortality in patients with sepsis compared with the Overt-Disseminated Intravascular Coagulation score and the Japanese Association for Acute Medicine Disseminated Intravascular Coagulation Score.[25] Research has demonstrated that the SOFA score was significantly higher in non-survivor groups than those that survived and it could predict the prognosis of septic patients.[24–26] The current findings demonstrated that the SOFA score was significantly higher in the non-survival group compared with the survival group and was superior to the APACHE II score, which was consistent with previous studies.[23–26] The ROC curve analysis demonstrated an AUC of 0.745 for the SOFA score, which suggests that the SOFA score may predict the short-term prognosis of the mortality in elderly patients with sepsis. The SOFA score may be better than the APACHE II score because sepsis is a life-threatening acute organ dysfunction caused by an imbalance in the inflammatory response. When compared with the APACHE II scoring system, the SOFA score more accurately reflects the overall acute state of the body

and is more suitable for the evaluation and prognosis of elderly patients with sepsis.

A previous study demonstrated that high levels of D-dimer can reflect a hypercoagulable state and secondary hyperfibrinolysis.[27] Some studies reported that the concentration of D-dimer in non-survival groups was higher than in survival groups and that using a combination of the SOFA score and high levels of D-dimer predicted 28-day mortality of sepsis patients.[28,29] These previous results were in agreement with the current findings that D-dimer was superior to the other biomarkers evaluated. The pathophysiological processes that occur in sepsis involve the release of inflammatory mediators, cytokines and endothelial cells, thereby activating and promoting the coagulation cascade, especially in disseminated intravascular coagulation.[30] Coagulation biomarkers accelerate the coagulation cascade, so the concentration of D-dimer and other coagulation-related biomarkers increases significantly.[31]

Sepsis is a systemic inflammatory reaction that occurs during infection, severe burns, multiple injuries and other diseases; and sepsis is the basis for the pathogenesis of MODS.[30] The lungs are commonly affected when multiple organ injuries are complicated by sepsis, resulting in acute respiratory distress syndrome (ARDS).[32] The Berlin diagnostic criteria can distinguish the severity of ARDS and PaO_2/FiO_2 is the most important feature of the criteria, which divides ARDS into mild, moderate and severe.[33] PaO_2/FiO_2 reflects the severity of the disease and the degree of lung damage in ARDS patients with sepsis.[34] A previous study found that PaO_2/FiO_2 is related to the occurrence of ARDS sepsis and PaO_2/FiO_2 in the non-survival group was significantly lower than that in the survival group.[35] PaO_2/FiO_2 was an independent risk factor for death in patients with sepsis.[35] These results were consistent with the current findings that PaO_2/FiO_2 had

prognostic value for predicting mortality in patients with sepsis.

The current study also had several limitations. First, it was a single-centre study undertaken at a tertiary referral hospital. Secondly, the current study only included a small number of elderly patients with sepsis, so the results may not be representative of the geriatric population. Thirdly, it was retrospective and not a prospective study, so the inherent bias of this study could not be avoided. Finally, some of the older patients that were transferred to the ICU had received prior sepsis management, such as fluid resuscitation, antibiotics and mechanical ventilation. Prospective controlled multi-centre studies are needed in the future.

In conclusion, this current study demonstrated that PaO_2/FiO_2, SOFA score and D-dimer can be used as prognostic makers for mortality in elderly patients with sepsis. The prognostic value of the combined PaO2/FiO2, SOFA and D-dimer levels in elderly patients with sepsis was higher than the values for the individual factors.

Author contributions

H.R.G. and Z.Y.S. provided the idea. X.L. collected data. W.Q.H., J.P.Z. and L.Z.T wrote the manuscript. L.X.Y. contributed to the scientific discussion. T.L. provided the design of the article, statistical consulting and data analysis.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

ORCID iD

Wan-Qin Hu https://orcid.org/0000-0003-2548-5801

References

1. Wei Y, Wang Z, Wang H, et al. Predicting population age structures of China, India, and Vietnam by 2030 based on compositional data. *PLoS One* 2019; 14: e0212772.

2. World Health Organization. China country assessment report on ageing and health, https://www.who.int/publications/i/item/9789241509312 (2015, 5 January 2019).

3. National Bureau of Statistics of China, http://www.stats.gov.cn/english/Statisticaldata/AnnualData/ (2018, 28 February 2019).

4. Thomas S A, Qiu Z, Chapman A, et al. Editorial: Chronic Illness and Ageing in China. *Front Public Health* 2020; 8: 104.

5. Flaatten H, de Lange DW, Artigas A, et al. The status of intensive care medicine research and a future agenda for very old patients in the ICU. *Intensive Care Med* 2017; 43: 1319–1328.

6. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315: 801–810.

7. Bail K, Berry H, Grealish L, et al. Potentially preventable complications of urinary tract infections, pressure areas, pneumonia, and delirium in hospitalised dementia patients: retrospective cohort study. *BMJ Open* 2013; 3: e002770.

8. Martin-Loeches I, Guia MC, Vallecoccia MS, et al. Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multicenter cohort study. *Ann Intensive Care* 2019; 9: 26.

9. Wu CC, Lan HM, Han ST, et al. Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis. *Ann Intensive Care* 2017; 7: 91.

10. Basile-Filho A, Lago AF, Menegueti MG, et al. The use of APACHE II, SOFA, SAPS 3, C-reactive protein/albumin ratio, and lactate to predict mortality of surgical critically ill patients: A retrospective cohort study. *Medicine (Baltimore)* 2019; 98: e16204.

11. Liu Z, Meng Z, Li Y, et al. 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.

12. Cui N, Zhang H, Chen Z, et al. 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* 2019; 47: 1573–1579.

13. Ryoo SM, Lee J, Lee YS, et al. Lactate Level Versus Lactate Clearance for Predicting Mortality in Patients With Septic Shock Defined by Sepsis-3. *Crit Care Med* 2018; 46: e489–e495.

14. Rimes-Stigare C, Frumento P, Bottai M, et al. Long-term mortality and risk factors for development of end-stage renal disease in critically ill patients with and without chronic kidney disease. *Crit Care* 2015; 19: 383.

15. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 207; 147: 573–577.

16. Remelli F, Castellucci F, Vitali A, et al. Predictive value of geriatric-quickSOFA in hospitalized older people with sepsis. *BMC Geriatr* 2021; 21: 241.

17. Davidson L, Hibberd P, Ruthzaer R, et al. Important Risk Factors Associated with 28-Day Mortality in Elderly Patients with Sepsis. In: *IDSA 2006, Health Care Epidemiology III: Geriatrics*, poster no. 1074, https://idsa.confex.com/idsa/2006/webprogram/Paper22417.html (2006, 25 January 2019).

18. Martin GS, Mannino DM and Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006; 34: 15–21.

19. Dombrovskiy VY, Martin AA, Sunderram J, et al. Rapid increase in hospitallization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* 2007 35: 1244–1250.

20. Esper AM, Moss M, Lewis CA, et al. The role of infection and comorbidity: Factors that influence disparities in sepsis. *Crit Care Med* 2006; 34: 2576–2582.

21. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; 395: 200–211.

22. Dwolatzky T Clarfield AM and Berman H. Non-specific presentations of illness. In: Jones R, Britten N, Culpepper L, Gass DA, Grol R, Mant D, Silagy C (eds) *Oxford Textbook of Primary Medical Care*. Oxford: Oxford University Press, 2003, pp.1247–1250.

23. Probst L, Schalk E, Liebregts T, et al. Prognostic accuracy of SOFA, qSOFA and SIRS criteria in hematological cancer patients: a retrospective multicenter study. *J Intensive Care* 2019; 7: 41.

24. Schoe A, Bakhshi-Raiez F, de Keizer N, et al. Mortality prediction by SOFA score in ICU-patients after cardiac surgery; comparison with traditional prognostic-models. *BMC Anesthesiol* 2020; 20: 65.

25. Iba T, Arakawa M, Mochizuki K, et al. Usefulness of Measuring Changes in SOFA Score for the Prediction of 28-Day Mortality in Patients With Sepsis-Associated Disseminated Intravascular Coagulation. *Clin Appl Thromb Hemost* 2019; 25: 1076029618824044.

26. Li Y, Yan C, Gan Z, et al. Prognostic values of SOFA score, qSOFA score, and LODS score for patients with sepsis. *Ann Palliat Med* 2020; 9: 1037–1044.

27. Semeraro F, Ammollo CT, Caironi P, et al. D-dimer corrected for thrombin and plasmin generation is a strong predictor of mortality in patients with sepsis. *Blood Transfus* 2020; 18: 304–311.

28. Tang N, Pan Y, Xu C, et al. Characteristics of emergency patients with markedly elevated D-dimer levels. *Sci Rep* 2020; 10: 7784.

29. Han YQ, Yan L, Zhang L, et al. Performance of D-dimer for predicting

sepsis mortality in the intensive care unit. *Biochem Med (Zagreb)* 2021; 31: 020709.

30. Gotts JE and Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ* 2016; 353: i1585.

31. Rodelo JR, De la Rosa G, Valencia ML, et al. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. *Am J Emerg Med* 2012; 30: 1991–1999.

32. Genga KR and Russell JA. Update of Sepsis in the Intensive Care Unit. *J Innate Immun* 2017; 9: 441–455.

33. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; 38: 1573–1582.

34. Fujishima S, Gando S, Saitoh D, et al. Demographics, Treatments, and Outcomes of Acute Respiratory Distress Syndrome: the Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORECAST) Study. *Shock* 2020; 53: 544–549.

35. Wang SB, Li T, Li YF, et al. The evaluation value of four scoring systems for the prognosis of patients with sepsis: a retrospective analysis of 311 cases. *Chinese Critical Care Medicine* 2017; 29: 133–138.