Research Letter

Incidence and outcomes of secondary infections in septic patients with cancer

Shi-ning Qu, Hai-jun Wang, Chu-lin Huang, Hao Zhang, Hao Wang, Zhen-nan Yuan, Xue-zhong Xing

Department of Intensive Care Unit, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Corresponding Author: *Xue-zhong Xing, Email: xingxuezhong@cicams.ac.cn*

World J Emerg Med 2022;13(5):400–402
DOI: 10.5847/wjem.j.1920-8642.2022.076

Secondary infections, also called intensive care unit (ICU)-acquired infections, are defined as infections occurring 48 h after admission to the ICU.[1] Critically ill patients are at a high risk of developing ventilator-associated pneumonia (VAP) and bloodstream infections (BSIs), which are associated with increased ICU mortality.[2]

Cancer patients are susceptible to infections owing to multiple risk factors due to immunosuppression, including radiotherapy, systemic therapy, and immunotherapy.[3,4] Hence, critically ill cancer patients with sepsis are also prone to developing secondary infections. In this study, we hypothesized that critically ill cancer patients with sepsis would develop more secondary infections, which would be associated with adverse outcomes.

METHODS

Inclusion criteria included patients who were diagnosed with sepsis and were admitted to the ICU for more than 48 h in the Cancer Hospital of the Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC) between November 2017 and October 2018. Patient data were retrospectively collected and reviewed. The exclusion criteria were patients who fulfilled the definition of sepsis but the length of stay (LOS) in the ICU was less than 48 h. The study was performed in line with the ethical *Declaration of Helsinki* in 1964 and its later amendments. The protocol was approved by the Institutional Review Boards of Cancer Hospital, Chinese Academy of Medical Sciences (22/092-3293). The patients' consent was waived due to the observational nature of this study.

The data included age, sex, modified Charlson's score, Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II), simplified acute physiology score 3 (SAPS 3) on ICU admission, preoperative radiotherapy/systemic therapy, American Joint Committee on Cancer (AJCC) tumor staging, and the presence of immunosuppression on admission. Outcome variables included the ventilation duration, ICU LOS, ICU death, hospital LOS, and in-hospital death. The secondary infection was defined as any new-onset infection occurring 48 h or more after admission to the ICU and intensivists starting a new antibiotic regimen.[1] Immunosuppression was defined as a lymphocyte count $<0.80\times10^9$/L according to the criteria.[5]

Statistical analyses were performed using SPSS software for Windows, version 16.0 (SPSS Inc., USA). Continuous variables are reported as the median (interquartile range) and compared using the Mann-Whitney *U*-test. Categorical variables are presented as absolute numbers (frequency percentages) and analyzed using the Chi-square test. The results were considered statistically significant when a two-tailed *P*-value <0.05.

RESULTS

A total of 161 patients with sepsis were admitted to the ICU during the study period. Of them, 14 (8.7%) patients developed secondary infections, including 6 pneumonia, 6 bloodstream infections, and 2 other infections. The univariable analysis demonstrated that compared with patients who developed secondary infections, those who did not develop secondary infections were more severe with higher APACHE II

scores (Table 1). No significant differences were noted in other clinical variables. Therefore, we did not perform a multivariable analysis further on the risk factors for secondary infections.

For outcomes, compared with patients who did not develop secondary infections, those who developed secondary infections had a significantly prolonged median ICU LOS (12 d vs. 6 d, *P*=0.004) and median hospital LOS (24 d vs. 17 d, *P*=0.021). Patients who developed secondary infections had insignificantly increased hospital mortality compared with those who did not develop secondary infections (14.3% [2/14] vs. 5.4% [8/147], *P*=0.190).

DISCUSSION

Secondary infections after admission to the ICU were reported to range from 13% to 29%.[1,6] No significant difference in the rate of secondary infections was observed between septic and non-septic patients. In this study, the incidence of secondary infections was 8%, which was lower than that reported in previous studies,[1,6] which could be attributed to patients' mild status in this study.

The risk factors for secondary infections include disease severity, shock, use of a central venous catheter, and mechanical ventilation.[1,6] However, we found an inverse association between disease severity and secondary infections. In a recent multicenter study, the rate of secondary pneumonia was higher in patients in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) group than in those in the influenza and no viral infection groups; however, simplified acute physiology score 2 and SOFA scores were lower in the SARS-CoV-2 group than in the other two groups.[7] A longer duration of mechanical ventilation could be responsible for this phenomenon. In our study, the median duration of mechanical ventilation was longer in patients in the secondary infection group than in those who did not develop secondary infections (11 d vs. 5 d, *P*=0.052). Therefore, adherence to preventive measures in VAP may be important to prevent the occurrence of secondary infections.[8]

A previous study demonstrated that patients with sepsis had impaired immunity, increasing their susceptibility to nosocomial infections.[9] In our study, 62.7% (101/161) of patients with sepsis had immunosuppression, as indicated by an absolute lymphocyte count of less than 0.80×10^9/L. However, secondary infections only occurred in eight patients (7.9%). Therefore, immunosuppression contributes only partly to nosocomial infections.[10] In our study, secondary infections were associated with prolonged median ICU LOS and median hospital LOS, which was consistent with the results of previous studies.[1,6] Therefore, prevention and treatment of secondary infections are important to reduce the ICU LOS and hospital LOS.

Our study had several limitations. First, compared with previous studies, the sample size was relatively small. Second, immunosuppression markers such as human leukocyte antigen DR and cytokines were not measured in patients with sepsis. Third, measures such as VAP and BSI preventive bundles were not documented.

CONCLUSIONS

In our study, approximately 8.7% of septic patients with cancer developed secondary infections. Secondary infections in septic patients with cancer were associated with longer ICU or hospital LOS. Disease severity and immunosuppression were not associated with the occurrence of secondary infection in critically ill cancer patients.

Table 1. Comparison of clinical characteristics between sepsis patients with secondary infections and those who did not develop secondary infections

Clinical variables	Non-secondary infections (*n*=147)	Secondary infections (*n*=14)	*P*-value
Age, years	63 (14)	63 (14)	0.488
Male	114 (77.6)	10 (71.4)	0.603
Modified Charlson's score	2 (1)	2 (0)	0.868
APACHE II	11 (7)	8 (8)	0.008
SAPS 3	52.50 (15.00)	47.50 (13.00)	0.118
SOFA	4.00 (4.00)	3.50 (1.00)	0.143
Radio/chemotherapy	50 (34.0)	3 (21.4)	0.338
AJCC tumor staging			0.804
Stage I/II	59 (39.5)	6 (42.9)	
Stage III/IV	89 (60.5)	8 (57.1)	
Immunosuppression at ICU admission	93 (63.3)	8 (57.1)	0.651
NLR at ICU admission	17.29 (19.70)	16.70 (12.01)	0.666
Septic shock	58 (39.5)	3 (21.4)	0.184

Data are reported as the median (interquartile range) or numbers (frequency percentages). APACHE II: Acute Physiology and Chronic Health Evaluation II; SAPS 3: simplified acute physiology score 3; SOFA: sequential organ failure assessment; AJCC: American Joint Committee on Cancer; ICU: intensive care unit; NLR: neutrophil-to-lymphocyte ratio.

Funding: The study was funded by the management research special fund of Cancer Hospital of Chinese Academy of Medical Sciences LC2020D01.

Ethical approval: The protocol was approved by the Institutional Review Boards of Cancer Hospital, Chinese Academy of Medical Sciences (22/092-3293).

Conflicts of interest: None declared.

Contributors: SNQ drafted the manuscript. All authors read and approved the final manuscript.

REFERENCES

1 van Vught LA, Klein Klouwenberg PM, Spitoni C, Scicluna BP, Wiewel MA, Horn J, et al. Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. JAMA. 2016;315(14):1469.
2 Lakbar I, Medam S, Ronflé R, Cassir N, Delamarre L, Hammad E, et al. Association between mortality and highly antimicrobial-resistant bacteria in intensive care unit-acquired pneumonia. Sci Rep. 2021;11(1):16497.
3 Zhao YX, Shen H, Yuan Y. Immunotherapy rechallenge for advanced non-small cell lung cancer. J Pract Oncol. 2021;36(3):202-8.
4 Xie F, Peng LL, Luo XY, Ji B. Preventive strategy for tumor patients during COVID-19 pandemic. J Pract Oncol. 2020; 35(2):123-6.
5 Darden DB, Brakenridge SC, Efron PA, Ghita GL, Fenner BP, Kelly LS, et al. Biomarker evidence of the persistent inflammation, immunosuppression and catabolism syndrome (PICS) in chronic critical illness (CCI) after surgical sepsis. Ann Surg. 2021;274(4):664-73.
6 Chen Y, Hu Y, Zhang J, Shen Y, Huang J, Yin J, et al. Clinical characteristics, risk factors, immune status and prognosis of secondary infection of sepsis: a retrospective observational study. BMC Anesthesiol. 2019;19(1):185.
7 Rouzé A, Martin-Loeches I, Povoa P, Makris D, Artigas A, Bouchereau M, et al. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: an European multicenter cohort study. Intensive Care Med. 2021;47(2):188-98.
8 Fortaleza CMCB, Filho SPF, Silva MO, Queiroz SM, Cavalcante RS. Sustained reduction of healthcare-associated infections after the introduction of a bundle for prevention of ventilator-associated pneumonia in medical-surgical intensive care units. Braz J Infect Dis. 2020;24(5):373-9.
9 Qiu Y, Tu GW, Ju MJ, Yang C, Luo Z. The immune system regulation in sepsis: from innate to adaptive. Curr Protein Pept Sci. 2019;20(8):799-816.
10 Angus DC, Opal S. Immunosuppression and secondary infection in sepsis: part, not all, of the story. JAMA. 2016;315(14):1457-9.

Received December 6, 2021
Accepted after revision May 20, 2022