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Pre-Sepsis Length of Hospital Stay and Mortality: A Nationwide Multicenter Cohort Study

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ABSTRACT

Background: Prolonged length of hospital stay (LOS) is associated with an increased risk of hospital-acquired conditions and worse outcomes. We conducted a nationwide, multicenter, retrospective cohort study to determine whether prolonged hospitalization before developing sepsis has a negative impact on its prognosis.
Methods: We analyzed data from 19 tertiary referral or university-affiliated hospitals between September 2019 and December 2020. Adult patients with confirmed sepsis during hospitalization were included. In-hospital mortality was the primary outcome. The patients were divided into two groups according to their LOS before the diagnosis of sepsis: early- (< 5 days) and late-onset groups (≥ 5 days). Conditional multivariable logistic regression for propensity score matched-pair analysis was employed to assess the association between late-onset sepsis and the primary outcome.
Results: A total of 1,395 patients were included (median age, 68.0 years; women, 36.3%). The early- and late-onset sepsis groups comprised 668 (47.9%) and 727 (52.1%) patients. Propensity score-matched analysis showed an increased risk of in-hospital mortality in the late-onset group (adjusted odds ratio [aOR], 3.00; 95% confidence interval [CI], 1.69–5.34). The same trend was observed in the entire study population (aOR, 1.85; 95% CI, 1.37–2.50). When patients were divided into LOS quartile groups, an increasing trend of mortality risk was observed in the higher quartiles (P for trend < 0.001).
Conclusion: Extended LOS before developing sepsis is associated with higher in-hospital mortality. More careful management is required when sepsis occurs in patients hospitalized for ≥ 5 days.

Keywords: In-Hospital Mortality; Late-onset Sepsis; Prolonged Hospitalization

INTRODUCTION

Sepsis is a life-threatening clinical condition with organ dysfunction caused by a dysregulated host response to infection.[1] It is a major public health concern, affecting approximately 49 million people each year and causing 11 million related deaths, accounting for up to 19.7%

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Disclosure

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Author Contributions

Conceptualization: Kim JY, Lee SM. Data curation: Kim JY, Lee HY, Oh DK, Lee SY. Formal analysis: Kim JY. Funding acquisition: Lim CM. Methodology: Kim JY, Lee HY, Lee SM. Project administration: Park MH, Lim CM. Resources: Park MH, Lim CM. Supervision: Lim CM, Lee SM. Writing - original draft: Kim JY. Writing - review & editing: Kim JY, Lee HY, Lee J, Oh DK, Lee SY, Park MH, Lim CM, Lee SM.

of all deaths worldwide.[2] The overall mortality rate of sepsis has been declining gradually over the years. Nevertheless, nearly 10% of patients still die of sepsis and for patients with septic shock, which is a subgroup of patients with sepsis with profound hypotension despite adequate volume resuscitation, the hospital mortality rate exceeds 40%.[1] Although our understanding of the pathophysiology of sepsis has improved over the past few decades, successful treatment options that have been shown to reduce mortality are still limited to timely fluid resuscitation and broad-spectrum antibiotic administration.[3,4] Consequently, preventative measures are imperative, as well as early detection through increased awareness, novel diagnostics, and therapeutics to improve the outcomes of sepsis.

While length of hospital stay (LOS) is affected by several factors, including disease severity, frailty, onset of complications, socioeconomic status, and family support,[5-9] prolonged hospitalization itself confers risks of unwanted adverse events, such as falls, nosocomial infection, decreased functional status, and malnutrition, eventually leading to worse patient outcomes.[10-12] Longer LOS has been reported to be associated with a higher adjusted mortality rate during and after hospitalization, as well as a higher risk of readmission in patients with chronic heart failure and acquired immunodeficiency syndrome.[13,14] With extended exposure to nosocomial pathogens and reduced physiological reserve due to preexisting illness, patients who develop sepsis after prolonged hospitalization may have a different host response than those who develop sepsis at an earlier stage. However, the impact of longer LOS on the clinical outcomes of sepsis has not been established.

We sought to improve the understanding of the clinical implications of LOS on hospital-acquired sepsis by examining its relationship with patient outcomes. We conducted the present study to test the hypothesis that prolonged hospitalization may lead to a worse prognosis for patients with hospital-acquired sepsis.

METHODS

Study population

We analyzed retrospectively collected data from 19 tertiary referral or university-affiliated hospitals between September 2019 and December 2020 as part of an ongoing nationwide, multicenter observational cohort study. The protocols for patient enrolment and data collection have been described previously.[15,16] For this study, consecutive patients older than 19 years and diagnosed with sepsis during hospitalization in general wards were included. The diagnosis of sepsis was based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[1] Those who were diagnosed with sepsis during their stay in the emergency room were excluded. Patients were followed up until death or hospital discharge.

Data collection and outcomes

Demographic and clinical factors potentially associated with mortality were collected at the time of sepsis diagnosis. These variables included age, sex, body mass index, comorbidities, Charlson comorbidity index score, clinical frailty score, Eastern Cooperative Oncology Group performance status, sequential organ failure assessment score, vital signs, and laboratory findings. The primary outcome was in-hospital mortality. For secondary outcomes, we evaluated intensive care unit (ICU) admission and ICU LOS. LOS before sepsis was defined as the interval from admission to sepsis diagnosis. For exploratory outcomes, sites of infection,

incidence of septic shock, antibiotics usage and its appropriateness, and implementation of other treatment modalities, such as surgical control of infectious sources, were also collected.

Statistical analysis

The patients were divided into two groups (early- and late-onset sepsis) according to their LOS before developing sepsis. Baseline characteristics were summarized as counts and proportions for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. Intergroup differences were compared using Pearson's χ^2 test or Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables as appropriate.

To accurately compare the two groups, we used propensity score matching methods to reduce the effects of confounding. The individual propensities for the occurrence of sepsis in the late stage of hospitalization (LOS ≥ 5 days) were calculated using factors that were representative of the underlying condition and disease severity of each patient at the time of sepsis diagnosis. These included age, sex, body mass index, initial admission ward (primarily medical or surgical unit), Eastern Cooperative Oncology Group performance status, clinical frailty score, sequential organ failure assessment score, Charlson comorbidity index, comorbidities (cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, hematologic malignancy, nonhematologic malignancy, diabetes, chronic neurological disorder, connective tissue disease, and immunocompromised status), vital signs (mean blood pressure, heart rate, respiratory rate, and body temperature), laboratory findings (white blood count, hemoglobin, hematocrit, platelet count, creatinine, and lactate), and the use of antibiotics before sepsis diagnosis. We conducted 1:1 propensity score matching without replacement. Adjusted with same covariates used to calculate the propensity score, conditional multivariable logistic regression for matched-pair analysis was conducted to determine the adjusted odds ratio (aOR) of late-onset sepsis for in-hospital mortality. Survival curves of the two groups were estimated using the Kaplan-Meier method and compared with the log-rank test. The survival period after the diagnosis of sepsis was used for this analysis.

For sensitivity analysis, we further divided patients into LOS quartile groups and compared the risk of the primary outcome in each quartile group. We also performed the same multivariable logistic regression analysis in the entire study cohort. Finally, we conducted an additional multivariable analysis, accounting for interventions related to source control, fluid therapy within 1 hour, hospital classification, and the site of infection. The statistical analyses were performed using R software, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided with an α of 0.05 for statistical significance.

Ethics statement

The present study was approved by the Institutional Review Board of Seoul National University Hospital (No. H-1808-135-967) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived because of the noninterventional retrospective observational nature of the study. We reported results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17]

RESULTS

Patient characteristics

A total of 1,395 patients were included in the analysis (median age, 68.0 years; women, 36.3%). The median LOS before the diagnosis of sepsis was 5.5 days (IQR, 1.2–15.8 days). Within a median LOS of 15.9 days (IQR, 8.2–31.0 days) after the diagnosis of sepsis, 480 (34.4%) patients had the primary outcome event (in-hospital death). With a cutoff value of 5 days rounded down from the median LOS before sepsis, 727 (52.1%) patients were included in the late-onset group and 668 (47.9%) in the early-onset group. The distribution of the patients' baseline characteristics in the two groups is shown in **Table 1**, both in the unmatched and propensity score-matched cases. In the unmatched sample, patients in the late-onset group were younger and had a higher proportion of hematologic malignancies, immunocompromised conditions, and prior antibiotic usage than those in the early-onset group. The proportion of patients with cardiovascular disease was higher in the early-onset group than in the late-onset group. Significantly more patients enrolled from tertiary general centers were in the late-onset group.

The distribution of the estimated propensity score for sepsis to occur at a later stage in both groups is shown in **Fig. 1**. In the matched cases, the early- and late-onset groups consisted of 406 patients each. The differences between the two groups were diminished in the propensity score-matched cases as compared with the unmatched population, with a standardized mean difference of < 0.1.

Infection characteristics by exposure to prolonged hospitalization

In the propensity score-matched cohort, the number of patients with pneumonia (34.0% vs. 29.1%; $P = 0.151$; **Table 2**) were similar between the two groups, whereas patients in the late-onset group had significantly higher number of catheter-related infection (4.9% vs. 1.0%; $P = 0.002$) and systemic infection without a definite portal of entry (14.0% vs. 8.4%; $P = 0.014$) and lower proportion of abdominal infection (34.5% vs. 45.1%; $P = 0.003$). The proportion of multidrug-resistant bacteria to be identified as causative pathogen were comparable between late- and early-onset groups (48.7% vs. 40.9%; $P = 0.202$).

Association between exposure to prolonged hospitalization and secondary and exploratory outcomes

In the propensity score-matched samples, there were no significant differences between late- and early-onset groups in septic shock, ICU admissions, and ICU LOS (**Table 3**). Furthermore, the use of appropriate empirical antibiotics within 24 hours, implementation of antibiotic combination therapy, adjunctive corticosteroids, and vasopressors were similar between the two groups. However, the use of interventions for source control was significantly higher in the early-onset group (21.2% vs. 15.3%; $P = 0.037$), whereas appropriate fluid therapy within 1 hour was higher in the late-onset group (90.4% vs. 85.5%; $P = 0.041$).

Association between exposure to prolonged hospitalization and the primary outcome

In propensity score-matched cases, in-hospital mortality was higher in the late-onset group than in the early-onset group (43.3% vs. 30.3%; $P < 0.001$) (**Table 4**). The conditional multivariable logistic regression for matched-pair analysis showed that late-onset sepsis was independently associated with higher incidence of in-hospital mortality (aOR, 3.00; 95% confidence interval [CI], 1.69–5.34; $P < 0.001$). When survival curves were estimated using

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Table 1. Baseline characteristics of study population, before and after propensity score matching

Characteristics	Unmatched patients				Propensity score-matched patients			
	Early-onset (LOS < 5 days) (n = 668)	Late-onset (LOS ≥ 5 days) (n = 727)	*P* value	SMD	Early-onset (LOS < 5 days) (n = 406)	Late-onset (LOS ≥ 5 days) (n = 406)	*P* value	SMD
Age, yr	69.0 (59.0–77.0)	66.0 (57.0–75.0)	0.006	0.164	69.0 (59.0–77.0)	70.0 (59.0–77.0)	0.765	0.018
Women	253 (37.9)	254 (34.9)	0.279	0.061	150 (36.9)	145 (35.7)	0.770	0.026
BMI, kg/m^2	22.2 (19.9–24.9)	22.1 (19.9–24.9)	0.958	0.006	22.2 (19.8–25.0)	21.9 (19.7–24.7)	0.527	0.024
Hospital LOS before sepsis, day	1.1 (0.3–2.4)	15.4 (9.2–29.0)	< 0.001		1.1 (0.3–2.5)	15.3 (8.8–28.9)	< 0.001	
Admission to medical ward	493 (73.8)	503 (69.2)	0.065	0.102	278 (68.5)	289 (71.2)	0.445	0.059
Clinical frailty score	4.0 (3.0–6.0)	4.0 (3.0–6.0)	0.217	0.063	4.0 (3.0–6.0)	4.0 (3.0–6.0)	0.796	0.015
Initial SOFA score	6.0 (4.0–9.0)	6.0 (4.0–9.0)	0.012	0.120	6.0 (4.0–9.0)	6.0 (4.0–9.0)	0.554	0.054
Initial ECOG performance status			0.113	0.109			0.943	0.023
0	147 (22.0)	155 (21.3)			90 (22.2)	90 (22.2)		
1	202 (30.2)	185 (25.4)			99 (24.4)	91 (22.4)		
2	143 (21.4)	151 (20.8)			91 (22.4)	93 (22.9)		
3	132 (19.8)	179 (24.6)			87 (21.4)	95 (23.4)		
4	44 (6.6)	57 (7.8)			39 (9.6)	37 (9.1)		
Charlson comorbidity index	6.0 (4.0–8.0)	5.0 (4.0–7.0)	0.099	0.065	6.0 (4.0–8.0)	6.0 (4.0–8.0)	0.746	0.038
Cardiovascular disease	169 (25.3)	149 (20.5)	0.038	0.114	89 (21.9)	84 (20.7)	0.732	0.030
Chronic lung disease	86 (12.9)	80 (11.0)	0.320	0.058	50 (12.3)	49 (12.1)	1.000	0.008
Chronic liver disease	97 (14.5)	88 (12.1)	0.211	0.071	61 (15.0)	54 (13.3)	0.546	0.049
Chronic kidney disease	105 (15.7)	103 (14.2)	0.461	0.043	55 (13.5)	57 (14.0)	0.919	0.014
Hematologic malignancy	50 (7.5)	187 (25.7)	< 0.001	0.505	43 (10.6)	53 (13.1)	0.328	0.076
Non-hematologic malignancy	310 (46.4)	309 (42.5)	0.158	0.079	203 (50.0)	211 (52.0)	0.623	0.039
Diabetes mellitus	243 (36.4)	247 (34.0)	0.377	0.050	150 (36.9)	148 (36.5)	0.942	0.010
Connective tissue disease	24 (3.6)	10 (1.4)	0.012	0.143	10 (2.5)	9 (2.2)	1.000	0.016
Immunocompromised state	28 (4.2)	71 (9.8)	< 0.001	0.220	23 (5.7)	19 (4.7)	0.635	0.044
Chronic neurologic disease	104 (15.6)	122 (16.8)	0.588	0.033	72 (17.7)	71 (17.5)	1.000	0.006
Initial vital signs								
Mean blood pressure, mmHg	67.7 (59.0–86.7)	69.0 (59.0–89.5)	0.244	0.058	66.7 (59.0–84.3)	66.7 (57.3–84.7)	0.696	0.031
Heart rate, /min	106.5 (88.5–124.0)	112.0 (96.0–130.0)	< 0.001	0.210	112.0 (93.0–127.0)	112.0 (94.0–128.0)	0.738	0.038
Respiratory rate, /min	22.0 (20.0–27.0)	22.0 (20.0–28.0)	0.294	0.026	22.0 (20.0–28.0)	22.0 (20.0–28.0)	0.923	0.020
Body temperature, ˚C	37.5 (36.7–38.3)	37.4 (36.6–38.3)	0.237	0.074	37.4 (36.6–38.3)	37.4 (36.6–38.3)	0.673	0.015
Initial laboratory results								
WBC, ·10^3/uL	9.4 (5.5–15.1)	8.6 (2.1–15.7)	0.001	0.108	9.6 (5.0–15.8)	9.7 (5.1–16.4)	0.875	0.029
Hb, g/dL	9.8 (8.5–11.6)	9.1 (8.0–10.5)	< 0.001	0.373	9.5 (8.3–11.0)	9.6 (8.4–10.9)	0.621	0.018
Hct, %	29.6 (25.7–35.0)	27.7 (24.0–32.0)	< 0.001	0.366	28.4 (25.2–33.2)	29.1 (25.3–32.9)	0.527	0.026
Plt, ·10^3/uL	140.0 (74.5–222.5)	110.0 (41.0–207.0)	< 0.001	0.192	129.0 (71.0–219.0)	135.0 (60.0–214.0)	0.785	0.015
Cr, mg/dL	1.2 (0.8–2.0)	1.1 (0.7–1.8)	0.001	0.140	1.2 (0.8–2.0)	1.1 (0.7–1.9)	0.162	0.031
Lactate, mmol/L	2.7 (1.7–4.8)	2.7 (1.6–4.8)	0.618	0.008	2.8 (1.7–5.0)	2.8 (1.6–5.0)	0.922	0.009
Antibiotics use before sepsis			< 0.001	0.277			0.096	0.017
No	229 (34.3)	144 (19.8)			98 (24.1)	95 (23.4)		
Yes	425 (63.6)	580 (79.8)			301 (74.1)	310 (76.4)		
Unknown	14 (2.1)	3 (0.4)			7 (1.7)	1 (0.2)		
Chemotherapy within 6 mon			0.001	0.206			0.430	0.091
Yes	73 (10.9)	129 (17.7)			55 (13.5)	62 (15.3)		
No	296 (44.3)	277 (38.1)			186 (45.8)	168 (41.4)		
Not applicable	299 (44.8)	321 (44.2)			165 (40.6)	176 (43.3)		
Hospital types			0.023	0.126			0.683	0.036
Tertiary centers	565 (84.6)	646 (88.9)			348 (85.7)	353 (86.9)		
General centers	103 (15.4)	81 (11.1)			58 (14.3)	53 (13.1)		
Rapid response team implemented	659 (98.7)	724 (99.6)	0.110	0.100	402 (99.0)	403 (99.3)	> 0.999	0.027

Values are presented as number (% or interquartile range).
Matched variables: age, sex, body mass index, admission to medical ward, clinical frailty score, initial SOFA score, ECOG performance status, Charlson comorbidity index, cardiovascular disease, chronic lung disease, chronic liver disease, chronic kidney disease, hematologic malignancy, non-hematologic malignancy, diabetes mellitus, connective tissue disease, immunocompromised state, chronic neurologic disease, white blood count, hemoglobin, hematocrit, platelet count, creatinine, lactate, mean blood pressure, heart rate, respiratory rate, body temperature, antibiotics use before sepsis.
LOS = length of hospital stay, SMD = standardized mean difference, BMI = body mass index, SOFA = sequential organ failure assessment, ECOG = Eastern Cooperative Oncology Group, WBC = white blood count, Hb = hemoglobin, Hct = hematocrit, Plt = platelet count, Cr = creatinine.

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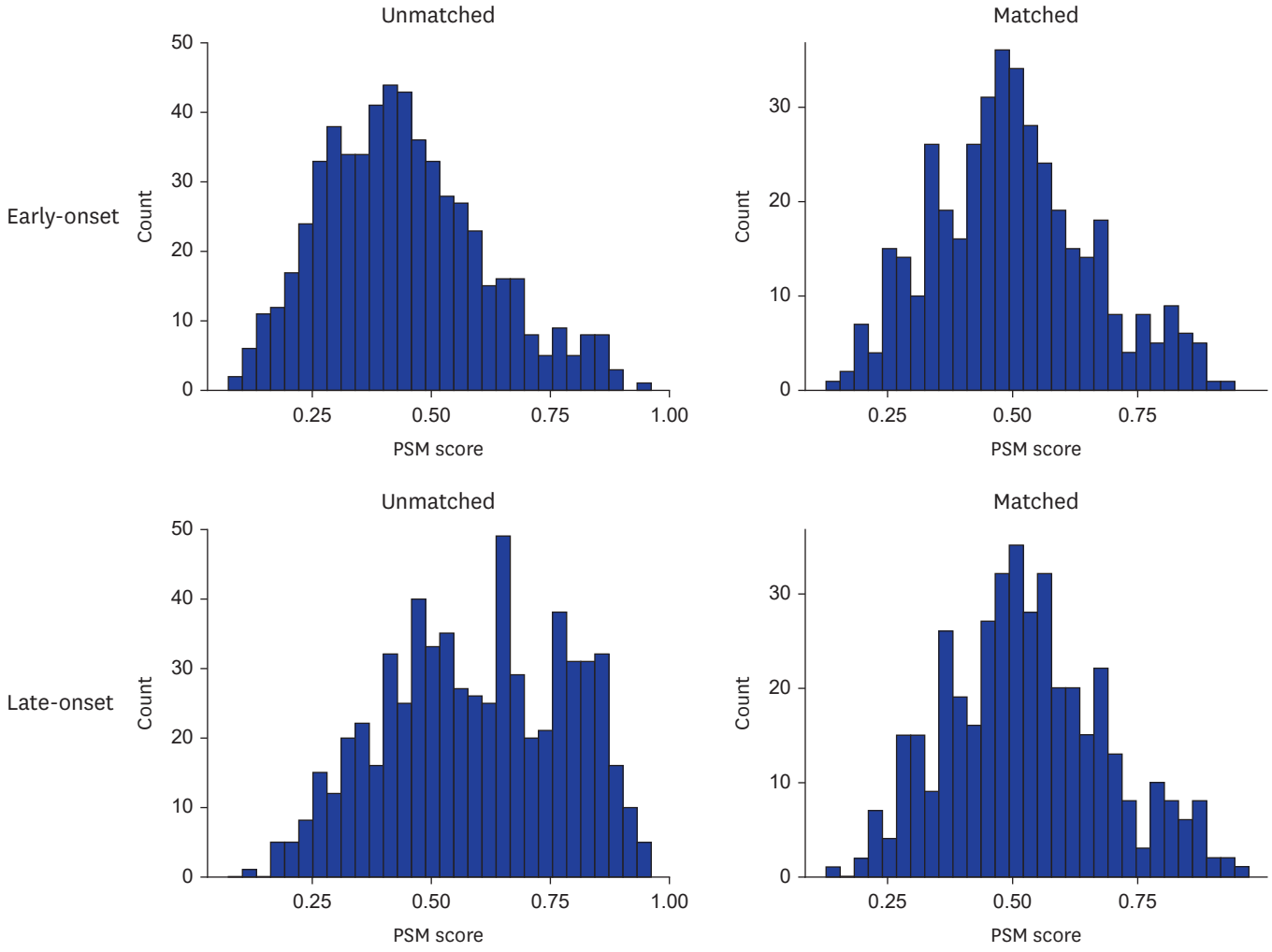

Fig. 1. The distribution of the estimated propensity score for patients to be exposed to prolonged hospitalization (length of hospital stay ≥ 5 days).

the Kaplan-Meier method, there was an evident separation between the early- and late-onset groups with median survival time of 67 vs. 47 days, respectively ($P = 0.011$; **Fig. 2**).

Sensitivity analyses

When patients were divided into quartiles according to their LOS before sepsis diagnosis for sensitivity analysis, in-hospital mortality was significantly higher in the highest LOS quartile group (aOR, 1.72; 95% CI, 1.24–2.38; $P < 0.001$; **Fig. 3**), whereas the lowest LOS quartile group showed a significant reduction of risk for the primary outcome (aOR, 0.67; 95% CI, 0.47–0.94; $P < 0.001$; **Fig. 3**). In the entire unmatched cohort, patients with exposure experienced higher proportion of in-hospital mortality compared to those with no exposure (41.0% vs. 27.2%; $P < 0.001$; **Table 4**). Multivariable analysis using data from the entire cohort showed similar association between the exposure and in-hospital mortality (aOR, 1.85; 95% CI, 1.37–2.50; $P < 0.001$; **Table 4**). When source control interventions, fluid therapy within 1 hour, hospital classification, and the site of infection were adjusted additionally in the multivariable analysis, late-onset group was still associated with increased mortality in both propensity score-matched (aOR, 3.03; 95% CI, 1.75–5.24; $P < 0.001$) and unmatched cohorts (aOR, 1.75; 95% CI, 1.29–2.39; $P < 0.001$) (**Table 4**).

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Table 2. Infection characteristics by exposure to prolonged hospitalization

Characteristics	Unmatched patients			Propensity score-matched patients		
	Early-onset (n = 668)	Late-onset (n = 727)	*P* value	Early-onset (n = 406)	Late-onset (n = 406)	*P* value
Site of primary infection						
Pulmonary	187 (28.0)	237 (32.6)	0.070	118 (29.1)	138 (34.0)	0.151
Abdominal	290 (43.4)	224 (30.8)	< 0.001	183 (45.1)	140 (34.5)	0.003
Urinary	98 (14.7)	79 (10.9)	0.040	61 (15.0)	43 (10.6)	0.074
Skin/Soft tissue	34 (5.1)	40 (5.5)	0.823	19 (4.7)	22 (5.4)	0.749
Catheter-related	7 (1.0)	33 (4.5)	< 0.001	4 (1.0)	20 (4.9)	0.002
Systemic infection	68 (10.2)	133 (18.3)	< 0.001	34 (8.4)	57 (14.0)	0.014
Pathogen identified	424 (63.5)	463 (63.7)	0.978	254 (62.6)	245 (60.3)	0.564
Gram positive bacteria	161 (40.0)	160 (37.6)	0.525	100 (41.3)	95 (42.4)	0.886
Gram negative bacteria	313 (77.7)	324 (76.1)	0.640	195 (80.6)	167 (74.6)	0.147
MDR bacteria			< 0.001			0.202
No	229 (56.8)	182 (42.7)		129 (53.3)	101 (45.1)	
Yes	148 (36.7)	222 (52.1)		99 (40.9)	109 (48.7)	
Multidrug resistant *Staphylococcus aureus*	29 (19.6)	33 (14.9)		16 (16.2)	17 (15.6)	
Multidrug resistant *Enterococcus* spp.	31 (20.9)	48 (21.6)		20 (20.2)	25 (22.9)	
Multidrug resistant *Enterobacteriaceae*	80 (54.1)	109 (49.1)		60 (60.6)	51 (46.8)	
Multidrug resistant *Pseudomonas* spp.	13 (8.8)	35 (15.8)		7 (7.1)	13 (11.9)	
Multidrug resistant *Acinetobacter*	17 (11.5)	18 (8.1)		11 (11.1)	12 (11.0)	

Values are presented as number (%).
MDR = multidrug resistant.

Table 3. Association between exposure to prolonged hospitalization and secondary and exploratory outcomes

Characteristics	Unmatched patients			Propensity score-matched patients		
	Early-onset (n = 668)	Late-onset (n = 727)	*P* value	Early-onset (n = 406)	Late-onset (n = 406)	*P* value
Intensive care unit admission	368 (55.1)	403 (55.4)	0.940	240 (59.1)	228 (56.2)	0.435
Intensive care unit length of stay, days	4.0 (2.0–10.0)	6.0 (2.0–12.0)	0.009	5.0 (2.0–11.0)	5.0 (2.0–11.0)	0.992
Septic shock	221 (33.1)	215 (29.6)	0.175	159 (39.2)	147 (36.2)	0.426
Appropriate empirical antibiotics < 24 hr			0.001			0.459
Yes	611 (91.5)	616 (84.7)		366 (90.1)	355 (87.4)	
Inappropriate	55 (8.2)	106 (14.6)		38 (9.4)	49 (12.1)	
Antibiotics combination therapy	448 (67.1)	531 (73.0)	0.017	284 (70.0)	299 (73.6)	0.275
Any intervention for source control	145 (21.7)	104 (14.3)	< 0.001	86 (21.2)	62 (15.3)	0.037
Surgical source control	49 (7.3)	38 (5.2)	0.130	29 (7.1)	19 (4.7)	0.180
Appropriate fluid therapy within 1 hr	579 (86.7)	653 (89.8)	0.081	347 (85.5)	367 (90.4)	0.041
Use of vasopressors	291 (43.6)	303 (41.7)	0.511	200 (49.3)	197 (48.5)	0.888
Adjunctive corticosteroid therapy	138 (20.7)	144 (19.8)	0.742	84 (20.7)	84 (20.7)	> 0.999

Values are presented as number (% or interquartile range).

DISCUSSION

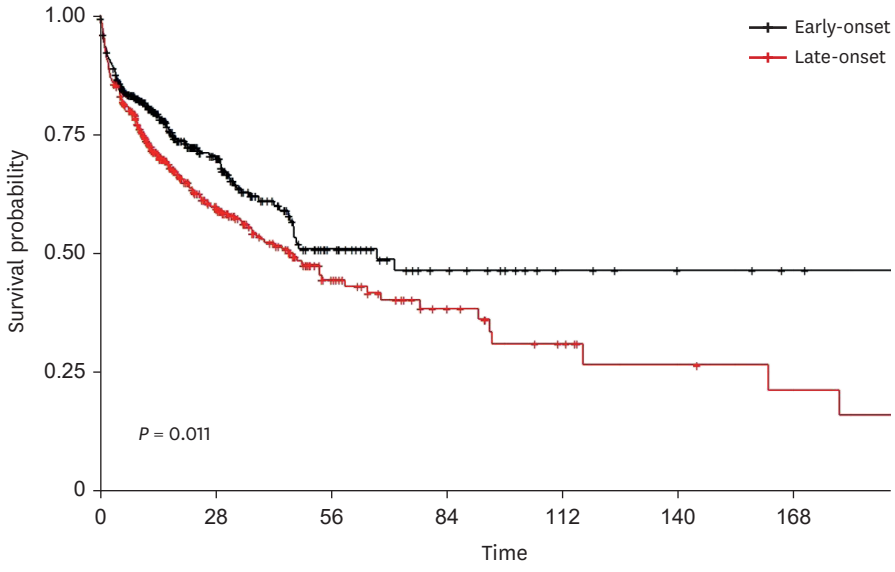
This analysis demonstrates that longer LOS before developing sepsis is associated with worse clinical outcomes. Patients with LOS ≥ 5 days before the diagnosis of sepsis had a higher risk of in-hospital death compared with patients who developed sepsis within 5 days of hospital stay. This association was sustained even after matching and adjusting for clinical characteristics as well as disease severity of patients between the two groups. Our findings suggest that sepsis which developed after a prolonged period of hospitalization may harbor characteristics different from those harbored by sepsis that has developed at an earlier stage, resulting in a worse prognosis.

The purpose of hospitalization is to provide concentrated monitoring, diagnostic, and therapeutic medical services in the hope of improving the quality of life and survival of patients. However, it is well established that these positive effects of hospitalization are always accompanied by adverse events, ranging from multidrug-resistant infections to

Table 4. Association between exposure to prolonged hospitalization and in-hospital mortality

Analysis	In-hospital mortality	*P* value
Propensity score-matched		
No. of events/No. of patients at risk		< 0.001
Early-onset group	123/406 (30.3)	
Late-onset group	176/406 (43.3)	
Multivariable analysis[a]	3.00 (1.69–5.34)	< 0.001
Sensitivity analysis[b]	3.03 (1.75–5.24)	< 0.001
Entire study cohort		
No. of events/No. of patients at risk		0.006
Early-onset group	134/458 (29.3)	
Late-onset group	346/937 (36.9)	
Multivariable analysis[a]	1.85 (1.37–2.50)	< 0.001
Sensitivity analysis[b]	1.75 (1.29–2.39)	< 0.001

Values are presented as number (%) or adjusted odds ratio (95% confidence interval).
[a]Adjusted for age, sex, body mass index, initial admission ward (primarily medical or surgical unit), Eastern Cooperative Oncology Group performance status, clinical frailty score, sequential organ failure assessment score, Charlson comorbidity index, comorbidities (cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, hematologic malignancy, nonhematologic malignancy, diabetes, chronic neurological disorder, connective tissue disease, and immunocompromised status), vital signs (mean blood pressure, heart rate, respiratory rate, and body temperature), laboratory findings (white blood count, hemoglobin, hematocrit, platelet count, creatinine, and lactate), and the use of antibiotics before sepsis diagnosis.
[b]Adjusted for the variables listed above and additionally for source control interventions, fluid therapy within 1 hour, hospital classification, and the site of infection.



No. at risk							
Early-onset	405	116	33	16	7	5	2
Late-onset	405	131	40	19	10	6	4

Fig. 2. Kaplan-Meier survival plot of late- and early-onset groups in the matched cohort. Survival curves of the late- and early-onset groups were estimated using the Kaplan-Meier method and compared with the log-rank test. The survival period after the diagnosis of sepsis was used.

delirium, physical deconditioning, and emotional distress.[18,19] For this reason, some physicians warn that hospitalization itself should be viewed as a procedure or intervention with inherent risks for all who receive it.[11] Along this line, to our knowledge, the present study for the first time demonstrates that prolonged hospitalization negatively affects the clinical outcomes of sepsis.

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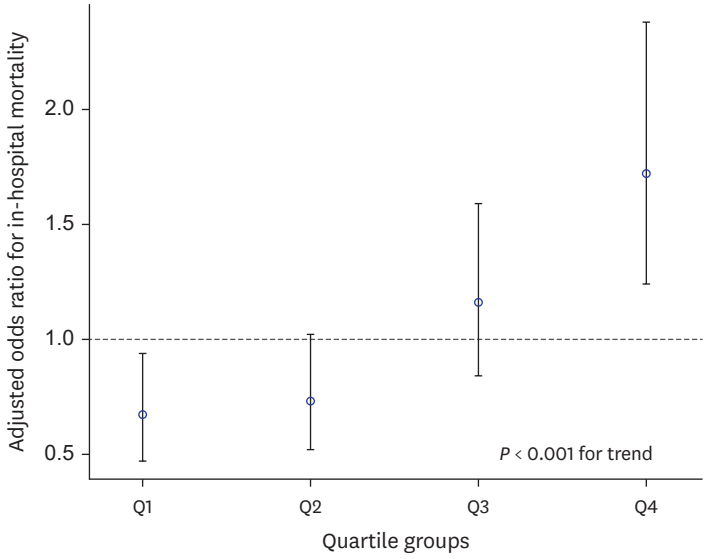

Fig. 3. Adjusted odds ratio for in-hospital mortality according to LOS quartile groups. Patients were divided into quartiles according to their hospital LOS (Q1: LOS < 1.17 days; Q2: 1.17 ≤ LOS < 5.55 days; Q3: 5.55 ≤ LOS < 15.81 days; Q4: LOS ≥ 15.81 days). Adjusted odds ratio for in-hospital mortality by quartile groups were Q1: 0.67 (95% CI, 0.47–0.94; *P* = 0.019), Q2: 0.73 (95% CI, 0.52–1.02; *P* = 0.066), Q3: 1.16 (95% CI, 0.84–1.59; *P* = 0.375), Q4: 1.72 (95% CI, 1.24–2.38; *P* = 0.001). *P* for trend calculated by generalized linear regression was < 0.001.
LOS = length of hospital stay, CI = confidence interval.

This worse prognosis associated with sepsis developing at a later stage of hospitalization is partially mediated by iatrogenic errors, such as catheter-related infection. In the propensity score-matched cohort, the proportion of catheter-related infection was significantly higher in the late-onset group (1.0% vs. 4.9%; *P* = 0.002). These untoward nosocomial infections, which can be prevented through collaborative efforts of careful interventions and active monitoring,[20] may have contributed to the occurrence of unwanted fatal events in the late-onset group. Nonetheless, catheter-related infection accounted for only 3.3% of all in-hospital deaths in our study and thus requires further explanation.

Several factors may have contributed to the observed increase in mortality among patients with prolonged hospitalization. Contrary to our initial expectations, there was no difference in the number of infections caused by multidrug-resistant bacteria between the two groups. In addition, the use of appropriate empirical antibiotics within 24 hours, implementation of antibiotic combination therapy, and the use of adjunctive corticosteroids and vasopressors were also similar. However, there was a higher proportion of catheter-related and systemic infections in the late-onset group whereas lower proportion of any kind of intervention for source control compared to the early-onset group. As a result, the delay in recognizing and intervening for these concealed infections may have partly contributed to the increased mortality. Furthermore, there may be patient-specific characteristics and underlying conditions not fully captured in the analysis, such as physical function, immune response, socioeconomic status, and family support that differed between the two groups. Further inquiry into these potential factors could help elucidate the reasons behind this disparity in mortality. In essence, this study revealed association rather than causality between sepsis occurring after prolonged hospitalization and higher mortality rates. This finding holds significance as a starting point for further research into why prolonged hospitalization occurs in the first place and how to mitigate sepsis occurrences following prolonged hospital stays.

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The present study findings have important implications for clinical practice. Although it is often onerous to determine the appropriate timing of discharge to avoid unnecessary extension of hospitalization while ensuring sufficient care, our findings provide evidence that prolonged hospital stay is not without risks. In our survival analysis using the survival period after the diagnosis of sepsis, patients in the late-onset group showed significantly worse prognoses than those in the early-onset group. When patients were divided into quartiles according to their LOS before the diagnosis of sepsis, the highest risk of in-hospital mortality was observed in the highest quartile, and vice versa. These findings emphasize the importance of shortening unnecessary hospital stays to prevent the occurrence of late-onset sepsis.

The present study has several limitations. First, although we adjusted for many potential variables between the early- and late-onset groups using a rigorous propensity score matching approach and multivariable analysis, the risk of unmeasured confounders, including socioeconomic status and family support, may be present in a nonrandomized study. Second, there was a substantial reduction in the sample size after the matching, which could limit the generalizability of the findings. However, our findings in the matched samples were consistently reproduced in the entire cohort. Third, because the primary focus of this study was to study the aftermath of sepsis, we lacked data before the diagnosis of sepsis. Consequently, we could not completely explain the reason for the prolonged hospitalization in the late-onset group. Also, we did not obtain information on long-term outcomes, such as 1-year mortality and readmission. Finally, being based on observational data, our findings do not serve as a proof that a reduction in the LOS would improve the survival of patients. However, dealing with an issue for which it is inherently difficult to design a randomized controlled study, our findings provide helpful guidance to clinicians who are trying to reduce their patients' LOS. Reduction in hospital stay, when done judiciously, may not violate the "do no harm" rule, but rather produce good outcome.

In conclusion, individuals with longer LOS before developing sepsis have a higher risk of in-hospital mortality than those who do not. Therefore, more careful management is required when sepsis occurs in a patient who has been hospitalized for ≥ 5 days, and it is advised to prevent unnecessary extension of hospitalization.

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REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315(8):801-10. PUBMED | CROSSREF
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395(10219):200-11. PUBMED | CROSSREF
3. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021;49(11):e1063-143. PUBMED | CROSSREF
4. Jarczak D, Kluge S, Nierhaus A. Sepsis-pathophysiology and therapeutic concepts. *Front Med (Lausanne)* 2021;8:628302. PUBMED | CROSSREF
5. Bein T, Hackner K, Zou T, Schultes S, Bösch T, Schlitt HJ, et al. Socioeconomic status, severity of disease and level of family members' care in adult surgical intensive care patients: the prospective ECSSTASI study. *Intensive Care Med* 2012;38(4):612-9. PUBMED | CROSSREF
6. Mudge AM, McRae P, Hubbard RE, Peel NM, Lim WK, Barnett AG, et al. Hospital-associated complications of older people: a proposed multicomponent outcome for acute care. *J Am Geriatr Soc* 2019;67(2):352-6. PUBMED | CROSSREF
7. Moore L, Cisse B, Batomen Kuimi BL, Stelfox HT, Turgeon AF, Lauzier F, et al. Impact of socio-economic status on hospital length of stay following injury: a multicenter cohort study. *BMC Health Serv Res* 2015;15(1):285. PUBMED | CROSSREF
8. White DB, Angus DC, Shields AM, Buddadhumaruk P, Pidro C, Paner C, et al. A randomized trial of a family-support intervention in intensive care units. *N Engl J Med* 2018;378(25):2365-75. PUBMED | CROSSREF
9. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010;210(6):901-8. PUBMED | CROSSREF
10. Ibrahim H, Harhara T, Athar S, Nair SC, Kamour AM. Multi-disciplinary discharge coordination team to overcome discharge barriers and address the risk of delayed discharges. *Risk Manag Healthc Policy* 2022;15:141-9. PUBMED | CROSSREF
11. Mao F, Greysen SR. Quantifying the risks of hospitalization-is it really as safe as we believe? *J Hosp Med* 2020;15(1):62-3. PUBMED | CROSSREF
12. Valente da Silva HG, Santos SO, Silva NO, Ribeiro FD, Josua LL, Moreira AS. Nutritional assessment associated with length of inpatients' hospital stay. *Nutr Hosp* 2012;27(2):542-7. PUBMED | CROSSREF
13. Ford N, Patten G, Rangaraj A, Davies MA, Meintjes G, Ellman T. Outcomes of people living with HIV after hospital discharge: a systematic review and meta-analysis. *Lancet HIV* 2022;9(3):e150-9. PUBMED | CROSSREF
14. Philbin EF, Roerden JB. Longer hospital length of stay is not related to better clinical outcomes in congestive heart failure. *Am J Manag Care* 1997;3(9):1285-91. PUBMED
15. Jeon K, Na SJ, Oh DK, Park S, Choi EY, Kim SC, et al. Characteristics, management and clinical outcomes of patients with sepsis: a multicenter cohort study in Korea. *Acute Crit Care* 2019;34(3):179-91. PUBMED | CROSSREF
16. Park S, Jeon K, Oh DK, Choi EY, Seong GM, Heo J, et al. Normothermia in patients with sepsis who present to emergency departments is associated with low compliance with sepsis bundles and increased in-hospital mortality rate. *Crit Care Med* 2020;48(10):1462-70. PUBMED | CROSSREF
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147(8):573-7. PUBMED | CROSSREF
18. Chang BP. Can hospitalization be hazardous to your health? A nosocomial based stress model for hospitalization. *Gen Hosp Psychiatry* 2019;60:83-9. PUBMED | CROSSREF
19. Schimmel EM. The hazards of hospitalization. *Ann Intern Med* 1964;60(1):100-10. PUBMED | CROSSREF
20. Pronovost PJ, Watson SR, Goeschel CA, Hyzy RC, Berenholtz SM. Sustaining reductions in central line-associated bloodstream infections in michigan intensive care units: a 10-year analysis. *Am J Med Qual* 2016;31(3):197-202. PUBMED | CROSSREF