Nature and Science of Sleep

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ORIGINAL RESEARCH

Sleep Disorder and Long-Term Mortality Among Sepsis Survivors: A Nationwide Cohort Study in South Korea

In-Ae Song[1,*]
Hye Yoon Park[2,3,*]
Tak Kyu Oh[1]

[1]Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; [2]Department of Psychiatry, Seoul National University Hospital, Seoul, South Korea; [3]Department of Psychiatry, College of Medicine, Seoul National University, Seoul, South Korea

*These authors contributed equally to this work

Background: We aimed to investigate the association of sleep disorder diagnosis among sepsis survivors with 5-year all-cause mortality.

Methods: Using the National Health Insurance Service (NHIS) database of South Korea, we included adult sepsis survivors who were primarily diagnosed with sepsis between 2011 and 2014 and survived for more than one year after diagnosis. The diagnosis of sleep disorders was evaluated using the International Classification of Diseases, 10th revision codes of G47* in the NHIS database.

Results: In total, 45,826 survivors of sepsis were included in this analysis. Among the sepsis survivors, 2935 (6.4%) were newly diagnosed with a sleep disorder within 1 year after the date of sepsis diagnosis, while 7938 (17.3%) were already diagnosed with sleep disorder before the date of sepsis diagnosis. In the multivariable Cox regression, the risk of 5-year all-cause mortality in the pre- and post-sepsis sleep disorder groups was 1.19-fold (hazard ratio: 1.19, 95% confidence interval: 1.14–1.24; $P<0.001$) and 1.79-fold (hazard ratio: 1.79, 95% confidence interval: 1.70–1.89; $P<0.001$) higher than that of the control group.

Conclusion: A 6.4% of sepsis survivors in South Korea were newly diagnosed with a sleep disorder within 1 year of sepsis diagnosis. Although both pre- and post-sepsis sleep disorders were associated with a higher 5-year all-cause mortality rate, the risk of the 5-year all-cause mortality in the post-sepsis sleep disorder group was higher than that in the pre-sepsis sleep disorder group.

Keywords: critical care, intensive care units, sepsis, survivors, sleep wake disorders

Introduction

Sepsis is characterized as a life-threatening condition attributable to a dysregulated host immune response to infection.[1] In the United States, it was reported that 6% of hospitalized adults had sepsis.[2] However, in-hospital mortality declined from 24.1% to 14.8% from 2010 to 2015[3,4] due to many efforts made to treat sepsis.[5] Recent cohort studies have reported that the improved survival for these patients was due to advancements in medical management and treatment.[6–8] Therefore, quality of life and return to work have emerged as important issues for survivors of sepsis.

Sleep is considered a physiological necessity, and sleep disorders are a common age-related problem that can lead to distress and discomfort, impaired daytime functioning, and serious complications.[9] Approximately 7.1–9.8% of the population in the United States have been diagnosed with a sleep disorder.[10,11] These patients with sleep disorders reportedly have a 1.5-fold higher mortality rate than the

Correspondence: Tak Kyu Oh
Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam, 13620, South Korea
Tel +82-31-787-7499
Email airohtak@hotmail.com

Received: 11 May 2021
Accepted: 21 June 2021
Published: 29 June 2021

general population with no sleep disorders.[11] Therefore, the prevention and treatment of sleep disorders have become important public health issues. A previous study reported that critically ill patients often suffer from sleep disturbances due to the development of delirium and the use of sedative agents during sepsis treatment.[12] Sleep disturbances manifest in the treatment during hospitalization and are a significant sequalae after discharge from the hospital among survivors.[13] Rundshage et al reported that sedated and ventilated critically ill patients discharged from intensive care units (ICUs) suffered from nightmares (9.3%) and hallucinations (6.6%).[14] In addition, it was reported that post-traumatic stress disorder (PTSD) related to ICU stays was associated with the development of amnesia and memory impairment after ICU discharge.[15] From these perspectives, sleep disorder development after sepsis can significantly affect the quality of daily life among sepsis survivors. However, the prevalence of sleep disorder development among sepsis survivors after sepsis treatment has not yet been studied, and its association with long-term prognosis remains controversial.

Therefore, we aimed to investigate the prevalence of sleep disorder diagnosis among sepsis survivors and identify its association with 5-year all-cause mortality. We hypothesized that pre- and post-sepsis sleep disorders were associated with a higher risk of 5-year all-cause mortality among sepsis survivors.

Materials and Methods

Ethical Statement and Data Source

This population-based cohort study was conducted according to the Reporting of Observational Studies in Epidemiology guidelines. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (X-1912-580-902) and the Health Insurance Review and Assessment Service (NHIS-2020-1-095). Informed consent was waived because data analyses were performed retrospectively using anonymized data extracted by an independent medical record technician at the South Korean National Health Insurance Service (NHIS) center unaffiliated with this study.

Study Population

We initially screened all adult patients (≥18 years of age) admitted to any hospital in South Korea between 2011 and 2014 for the main diagnosis of sepsis (A40, A41) or septic shock (R65.2), according to the International Classification of Diseases, 10th revision (ICD-10) codes. The NHIS database contains all newly registered disease diagnoses made during hospitalization, and the diagnosis registered as the primary morbidity of treatment is then classified as the main diagnosis. That is, if a patient initially admitted with a diagnosis of urinary tract infection was diagnosed as sepsis during treatment, the main diagnosis of the patient would be classified as sepsis, by NHIS. If a patient was admitted to any hospital for sepsis treatment two times or more during the study period, only the first episode was included in the study. Among all patients who were mainly diagnosed with sepsis during hospitalization, those identified as sepsis survivors (ie, those who had survived for over 365 days after sepsis diagnosis) were eligible for inclusion in this study.

Sleep Disorder as a Main Independent Variable

The diagnosis of sleep disorders was evaluated using the ICD-10 codes of G47* (G47.0: primary insomnia, and G47.1-9) in the NHIS database. The sepsis survivors were classified into the following three groups: 1) Pre-sepsis sleep disorder group, diagnosed with sleep disorder before the date of diagnosis of sepsis; 2) post-sepsis sleep disorder group, with no prior history of sleep disorders, but newly diagnosed with a sleep disorder within 1 year of sepsis diagnosis; and 3) control group, not diagnosed with a sleep disorder before or after the date of diagnosis of sepsis.

Endpoint

The primary endpoint of this study was 5-year all-cause mortality (additional 4-year all-cause mortality) among survivors of sepsis, defined as any death of survivors of sepsis after the diagnosis of sepsis within 5 years. The survival times of sepsis survivors were calculated from the date of sepsis diagnosis to the date of death or April 1, 2020 because the mortality dates were extracted until December 31, 2019.

Covariates

Data extracted as confounders included demographic characteristics (age and sex) and place of residence at the time of diagnosis (Seoul, metropolitan city, other areas, and unknown). The annual income level of sepsis survivors in terms of the Korean currency (Won) was extracted and

classified into five groups based on quartile ratio (Q1: lowest, Q2, Q3, Q4: highest, and unknown group). To reflect the severity of sepsis patients, endotracheal intubation, continuous vasopressor infusion, mechanical ventilatory support, continuous renal replacement (CRRT) use, and extracorporeal membrane oxygenation (ECMO) use during sepsis treatment were collected as confounders. The vasopressor infusion includes the infusion of epinephrine, norepinephrine, vasopressin, dopamine, and dobutamine. Data on the total sepsis treatment duration was categorized into four groups (1–7, 8–15, 16–30, and >30 days). Information regarding how the sepsis survivor was followed up after hospital discharge was divided into three groups as follows: 1) follow-up in the same hospital, 2) referred to another hospital for admission, and 3) outpatient clinic follow-up. To reflect the comorbid status at the diagnosis of sepsis, we used the underlying disability before sepsis and the Charlson comorbidity index. The ICD-10 codes calculated for determining the Charlson score before sepsis treatment are presented in Appendix 1, and the ICD-10 codes for pre-sepsis were extracted from within 1 year prior to sepsis diagnosis. In addition, underlying depression (ICD-10 codes: F32, F33, F34.1) and PTSD (ICD-10 codes: F43*) were extracted and included as covariates for adjustment because sleep disorder is known to be often accompanied by PTSD or depression.[16,17] Regarding sleeping pills, the prescription information of benzodiazepines and Z-drugs (zaleplon, zopiclone, eszopiclone, and zolpidem) was extracted and used as covariates for adjustment. If a sepsis survivor was prescribed the drugs for over 30 days, he/she was defined as a benzodiazepine or Z-drug user.

Statistical Analysis

Baseline characteristics of sepsis survivors are presented as means with standard deviations for continuous variables and numbers with percentages for categorical variables. First, we compared the baseline characteristics between the three groups using a one-way ANOVA test for continuous variables and the chi-square test for categorical variables. Second, we constructed a multivariable Cox regression model to investigate whether sleep disorder before or after sepsis affected the risk of 5-year all-cause mortality. In the multivariable model, the risk of 5-year all-cause mortality in the pre-sepsis sleep disorder group and post-sepsis sleep disorder group was compared to that of the control group. All covariates were included in the multivariable model for adjustment. Third, a separate multivariable Cox regression model was constructed to examine the risk of 5-year all-cause mortality in pre- and post-sepsis insomnia and the other sleep disorder group compared to that of the control group. Fourth, we performed sensitivity analyses of the multivariable Cox regression model for 5-year all-cause mortality according to sleep disorder with depression or PTSD and sleep disorder with benzodiazepines or Z-drug use. Sleep disorder is commonly accompanied by PTSD or depression,[16,17] and benzodiazepines or Z-drug use might affect long-term mortality in patients with sleep disorders.[18] Therefore, sensitivity analyses are needed to confirm the impact of PTSD or depression and benzodiazepine or Z-drug use on the outcomes in this study. Multivariable Cox regression modeling was used for the subgroup analyses using the same method as the main analysis. The results of the Cox model were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and confirmed using log-log plots that the central assumption of the multivariable Cox regression model was satisfied. C-statistics were used to identify the C-index of the multivariable Cox regression model, and there was no collinearity between the variables in the model (variance inflation factor <2.0). All statistical analyses were performed using R software (version 4.0.3 with R packages, the R Project for Statistical Computing, Vienna, Austria), and values of $P<0.05$ were considered statistically significant.

Results

Study Population

From 2011 to 2014, 149,278 patients were diagnosed with sepsis and admitted to hospitals 284,556 times for treatment. Among these patients, 93,722 (62.8%) were alive for more than one year after sepsis diagnosis; accordingly, they were defined as survivors of sepsis. Subsequently, we excluded 47,896 pediatric patients (<18 years old) from the analysis. Finally, a total of 45,826 survivors of sepsis, alive for more than one year after sepsis diagnosis, were included in this analysis (Figure 1). The baseline characteristics of the sepsis survivors in this study are presented in Table 1. Among the sepsis survivors, 2935 (6.4%) were newly diagnosed with a sleep disorder within 1 year after the date of sepsis diagnosis and defined as the post-sepsis sleep disorder group, while 7938 (17.3%) were already diagnosed with sleep disorder before the date of sepsis diagnosis and defined as the pre-sepsis sleep disorder group. The prevalence of insomnia was 11.2% (5120/

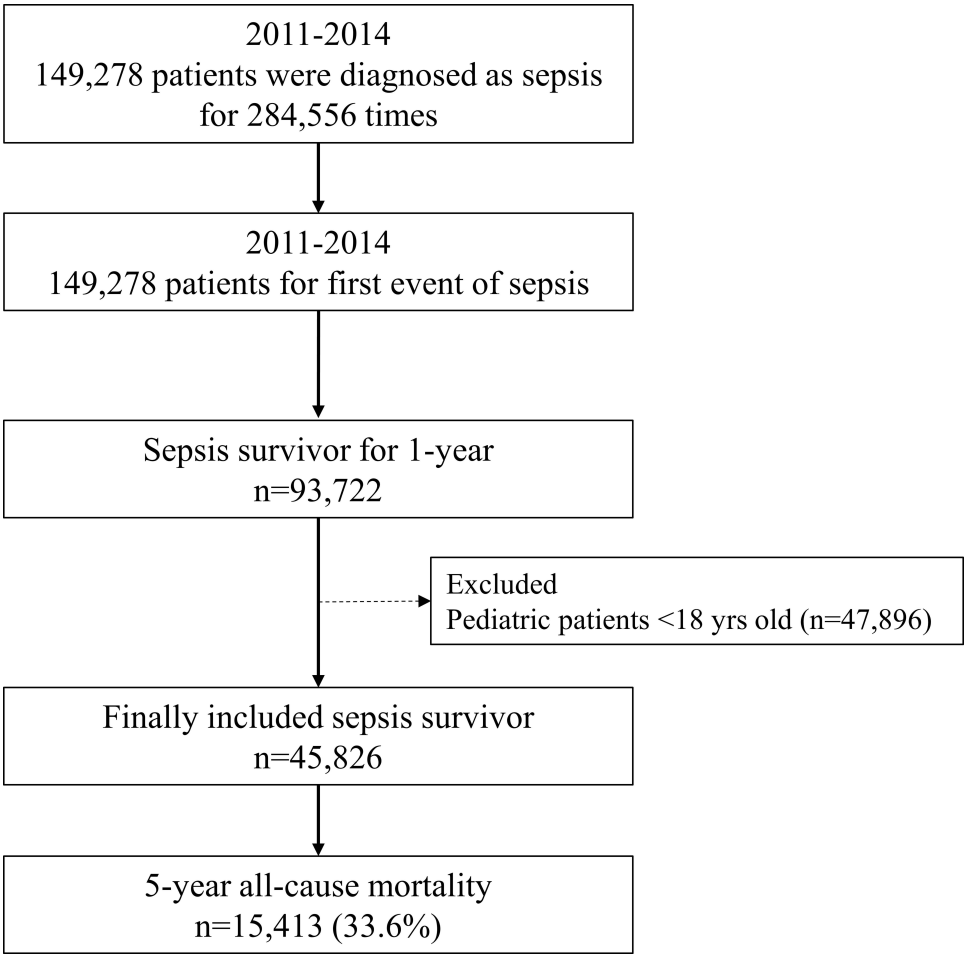

Figure 1 Flow chart depicting patient selection.

45,826) and 4.3% (1988/45,826) in pre- and post-sepsis sleep disorder groups, respectively.

Five-Year All-Cause Mortality

Table 2 shows the results of the comparison of characteristics between the three groups among sepsis survivors. The 5-year all-cause mortality rate was 47.0% (6536/45,826) in the pre-sepsis sleep disorder group, 40.5% (1678/45,826) in the post-sepsis sleep disorder group, and 25.9% (7199/45,826) in the control group. In the multivariable Cox regression model 1 (Table 3), the risk of 5-year all-cause mortality in the pre- and post-sepsis sleep disorder groups was 1.19-fold (HR:1.19, 95% CI: 1.15–1.24; $P<0.001$) and 1.79-fold (HR:1.79, 95% CI: 1.70–1.89; $P<0.001$) higher than that of the control group. In the multivariable Cox regression model 2, the pre-sepsis insomnia group and other sleep disorder group showed a 1.15-fold (HR:1.15, 95% CI: 1.10–1.23; $P<0.001$) and a 1.05-fold (HR:1.05, 95% CI: 1.03–1.06; $P=0.014$) higher 5-year all-cause mortality risk than the control group, respectively. In addition, the post-sepsis insomnia group and other sleep disorder group showed a 1.89-fold (HR:1.89, 95% CI: 1.85–1.94; $P<0.001$) and a 1.44-fold (HR:1.44, 95% CI: 1.39–1.48; $P<0.001$) higher 5-year all-cause mortality risk than the control group, respectively. The C-index of the multivariable model was 0.82 (95% CI: 0.81–0.82). The survival plot derived from the multivariable Cox regression model showed a similar trend, as shown in Appendix 2.

Sensitivity Analyses

Table 4 shows the results of sensitivity analyses of the multivariable Cox regression model for 5-year all-cause mortality according to sleep disorder with depression or PTSD and sleep disorder with benzodiazepines or Z-drug use. Compared to the control group (multivariable model 1), the pre-sepsis sleep disorder group was associated with 1.19-fold (HR: 1.19, 95% CI: 1.13–1.25; $P<0.001$) and 1.21-fold (HR: 1.21, 95% CI: 1.13–1.29; $P<0.001$) higher 5-year all-

Table 1 Baseline Characteristics of Total Sepsis Survivor from 2011 to 2014 (n=45,826)

Variable	N (%)	Mean (SD)
Age, year		62.9 (19.3)
Gender, Male	19,055 (41.6)	
Residence at diagnosis of sepsis		
Seoul (Capital city)	10,859 (23.7)	
Other metropolitan city	8296 (18.1)	
Other area	26,671 (58.2)	
Income level at diagnosis of sepsis		
Q1 (Lowest)	6993 (15.3)	
Q2	6793 (14.8)	
Q3	9111 (19.9)	
Q4 (Highest)	15,408 (33.6)	
Unknown	7521 (16.4)	
Underlying disability before sepsis	11,843 (25.8)	
Charlson comorbidity index before sepsis		4.8 (3.7)
Total treatment duration for sepsis, day		
1–7	22,893 (50.0)	
8–15	10,655 (23.3)	
16–30	8258 (18.0)	
> 30	4020 (8.8)	
Treatment of sepsis during hospitalization		
Mechanical ventilator use	2295 (5.0)	
Endotracheal intubation	1771 (3.9)	
CRRT use	491 (1.1)	
Vaspressor use	3255 (7.1)	
ECMO use	12 (0.0)	
Follow up after discharge		
Follow up in the same hospital	29,438 (64.2)	
Referred to other hospital for admission	2039 (4.4)	
Outpatient clinic follow up	14,349 (31.3)	
Year of diagnosis of sepsis		
2011	10,205 (22.3)	
2012	10,958 (23.9)	
2013	11,436 (25.0)	
2014	13,227 (28.9)	
Underlying PTSD	72 (0.2)	
Underlying depression	10,731 (23.4)	
BDZ or Z-drug user	4191 (9.1)	
Sleep disorder before and after sepsis		
Control group	34.953 (76.3)	
Pre-sepsis sleep disorder group	7938 (17.3)	
Insomnia	5120 (11.2)	
Other sleep disorder	2818 (6.1)	
Post-sepsis sleep disorder group	2935 (6.4)	
Insomnia	1988 (4.3)	
Other sleep disorder	947 (2.1)	

Abbreviations: SD, standard deviation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; PTSD, post-traumatic stress disorder; BDZ, benzodiazepine.

cause mortality rate without and with PTSD or depression, respectively. The post-sepsis sleep disorder group was associated with 1.67-fold (HR: 1.67, 95% CI: 1.56–1.79; $P<0.001$) and 2.01-fold (HR: 2.01, 95% CI: 1.84–2.19; $P<0.001$) higher 5-year all-cause mortality rate without and with PTSD or depression, respectively. In addition, compared to the control group (multivariable model 2), the pre-sepsis sleep disorder group was associated with 1.18-fold (HR: 1.18, 95% CI: 1.13–1.23; $P<0.001$) and 1.30-fold (HR: 1.30, 95% CI: 1.18–1.43; $P<0.001$) higher 5-year all-cause mortality rate without and with benzodiazepines or Z-drug use, respectively. Furthermore, the post-sepsis sleep disorder group was associated with 1.76-fold (HR: 1.76, 95% CI: 1.66–1.86; $P<0.001$) and 2.02-fold (HR: 2.02, 95% CI: 1.77–2.30; $P<0.001$) higher 5-year all-cause mortality rate without and with benzodiazepines or Z-drug use, respectively.

Discussion

This population-based cohort study showed that 6.4% (2935 of 34,953) of sepsis survivors were newly diagnosed with a sleep disorder within 1 year after sepsis diagnosis. Additionally, sleep disorders both pre- and post-sepsis were associated with a higher 5-year all-cause mortality rate among sepsis survivors. Interestingly, this association was more evident among patients in the post-sepsis sleep disorder group, sleep disorder group with PTSD or depression, and sleep disorder group with benzodiazepine or Z-drug use. Our results are important because this is the first study reporting the prevalence of sleep disorders among survivors of sepsis and its association with long-term mortality.

In a prospective international survey of 1731 sepsis survivors by Huang et al,[19] it was reported that many survivors of sepsis suffered from sleep disturbances. However, the exact prevalence of sleep disorders was not reported in this study.[19] In another systemic review, the prevalence of sleep disorders varied from 10–61% among ICU survivors who were admitted to the hospital for treatment of a critical illness.[20] Most previous studies have reported prevalence based on questionnaires,[19,20] while our study reported the prevalence of pre- and post-sepsis sleep disorder diagnosis using registered ICD-10 codes in the NHIS database. Therefore, it is possible that only patients diagnosed with a definite sleep disorder were included in our study, and the result should be interpreted carefully.

Table 2 Comparision of Characteristics Between Three Groups Among Sepsis Survivors

Variable	Control Group n=34,953	Pre-Sepsis Sleep Disorder n=7938	Post-Sepsis Sleep Disorder n=2935	*P*-value
Age, year	60.7 (19.9)	70.2 (14.8)	69.6 (15.7)	<0.001
Gender, Male	12,485 (44.9)	4819 (34.7)	1751 (42.2)	<0.001
Residence at diagnosis of sepsis				<0.001
Seoul (Capital city)	7444 (26.8)	2569 (18.5)	846 (20.4)	
Other metropolitan city	4587 (16.5)	2903 (20.9)	806 (19.4)	
Other area	15,747 (56.7)	8430 (60.6)	2494 (60.2)	
Income level at diagnosis of sepsis				<0.001
Q1 (Lowest)	4268 (15.4)	2060 (14.8)	665 (16.0)	
Q2	4524 (16.3)	1680 (12.1)	589 (14.2)	
Q3	5958 (21.4)	2398 (17.2)	755 (18.2)	
Q4 (Highest)	9090 (32.7)	4963 (35.7)	1355 (32.7)	
Unknown	3938 (14.2)	2801 (20.1)	782 (18.9)	
Underlying disability before sepsis	5684 (20.5)	4919 (35.4)	1240 (29.9)	<0.001
Charlson comorbidity index before sepsis	4.5 (3.7)	6.0 (3.6)	6.1 (3.9)	<0.001
Treatment of sepsis during hospitalization				
Mechanical ventilator use	1518 (4.3)	573 (7.2)	204 (7.0)	<0.001
Endotracheal intubation	1167 (3.3)	456 (5.7)	148 (5.0)	<0.001
CRRT use	344 (1.0)	107 (1.3)	40 (1.4)	0.005
Vaspressor use	2268 (6.5)	764 (9.6)	223 (7.6)	<0.001
ECMO use	6 (0.0)	4 (0.1)	2 (0.1)	0.089
Total treatment duration for sepsis, day				<0.001
1–7	15,952 (57.4)	5393 (38.8)	1548 (37.3)	
8–15	5506 (19.8)	4049 (29.1)	1100 (26.5)	
16–30	4386 (15.8)	2930 (21.1)	942 (22.7)	
> 30	1934 (7.0)	1530 (11.0)	556 (13.4)	
Follow up after discharge				<0.001
Follow up in the same hospital	18,724 (67.4)	8394 (60.4)	2320 (56.0)	
Referred to other hospital for admission	1102 (4.0)	687 (4.9)	250 (6.0)	
Outpatient clinic follow up	7952 (28.6)	4821 (34.7)	1576 (38.0)	
Underlying depression or PTSD	6570 (18.8)	3142 (39.6)	1057 (36.0)	<0.001
BDZ or Z-drug user	2135 (6.1)	1529 (19.3)	503 (17.1)	<0.001
Year of diagnosis of sepsis				<0.001
2011	6955 (25.0)	2242 (16.1)	1008 (24.3)	
2012	6838 (24.6)	3115 (22.4)	1005 (24.2)	
2013	6594 (23.7)	3827 (27.5)	1015 (24.5)	
2014	7391 (26.6)	4718 (33.9)	1118 (27.0)	
5-year all-cause mortality	7199 (25.9)	6536 (47.0)	1678 (40.5)	<0.001

Note: Presented as number with percentage or mean with standard deviation.
Abbreviations: CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; PTSD, post-traumatic stress disorder; BDZ, benzodiazepine.

Recently, we reported that adult individuals with sleep disorders were associated with a 1.23-fold higher 5-year all-cause mortality than adult individuals without sleep disorders among the South Korean population.[21] In our study, the 5-year all-cause mortality among sepsis survivors with pre- and post-sepsis sleep disorder showed a 1.19-fold and a 1.79-fold increase in the 5-year all-cause mortality, respectively. It suggested that the higher

Table 3 Multivariable Cox Model for 5-Year All-Cause Mortality Among Sepsis Survivor

Variable	Multivariable Cox Model	P-value
	HR (95% CI)	
Sleep disorder before and after sepsis (model 1)		
Control group	1	
Pre-sepsis sleep disorder group	1.19 (1.15, 1.24)	<0.001
Post-sepsis sleep disorder group	1.79 (1.70, 1.89)	<0.001
Sleep disorder before and after sepsis (model 2)		
Control group	1	
Pre-sepsis insomnia group	1.15 (1.10, 1.23)	<0.001
Pre-sepsis other sleep disorder group	1.05 (1.03, 1.06)	0.014
Post-sepsis insomnia group	1.89 (1.85, 1.94)	<0.001
Post-sepsis other sleep disorder group	1.44 (1.39, 1.48)	<0.001
Age, year	1.06 (1.06, 1.06)	<0.001
Gender, Male	1.50 (1.45, 1.55)	<0.001
Residence at diagnosis of sepsis		
Seoul (Capital city)	1	
Other metropolitan city	1.11 (1.05, 1.17)	<0.001
Other area	1.08 (1.03, 1.12)	0.001
Income level at diagnosis of sepsis		
Q1 (Lowest)	1	
Q2	0.97 (0.91, 1.03)	0.360
Q3	0.95 (0.90, 1.00)	0.069
Q4 (Highest)	0.93 (0.88, 0.98)	0.003
Unknown	1.18 (1.11, 1.24)	<0.001
Underlying disability before sepsis	1.45 (1.40, 1.07)	<0.001
Charlson comorbidity index before sepsis, point	1.06 (1.06, 1.07)	<0.001
Treatment of sepsis during hospitalization		
Mechanical ventilator use	1.35 (1.22, 1.51)	<0.001
Endotracheal intubation	0.94 (0.83, 1.05)	0.277
CRRT use	0.77 (0.66, 0.89)	0.001
Vaspressor use	0.89 (0.83, 0.95)	<0.001
ECMO use	1.72 (0.64, 4.59)	0.283
Total treatment duration for sepsis, day		
1–7	1	
8–15	1.46 (1.40, 1.52)	<0.001
16–30	1.36 (1.29, 1.42)	<0.001
> 30	1.50 (1.41, 1.59)	<0.001
Follow up after discharge		
Follow up in the same hospital	1	
Referred to other hospital for admission	0.82 (0.76, 0.88)	<0.001
Outpatient clinic follow up	0.63 (0.60, 0.65)	<0.001
Underlying depression or PTSD	1.00 (0.99, 1.01)	0.190
BDZ or Z-drug user	1.00 (0.99, 1.00)	0.522
Year of diagnosis of sepsis		
2011	1	
2012	0.88 (0.84, 0.92)	<0.001
2013	0.88 (0.84, 0.92)	<0.001
2014	0.84 (0.80, 0.88)	<0.001

Notes: C-index: 0.82 (0.81, 0.82). Model fitting information: −2 log likeliwood 308843.0, Chi-square: 13529.0, *P*<0.001.

Abbreviations: HR, hazard ratio; CI, confidence interval; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; PTSD, post-traumatic stress disorder; BDZ, benzodiazepine.

risk of long-term mortality among sepsis survivors with sleep disorders was not much different from that in the general adult population of South Korea.

Additionally, the role of PTSD among survivors of sepsis might affect the results of this study. In a recent meta-analysis, the overall prevalence of PTSD symptoms among adult critical care survivors was 19.8%.[22] For sepsis patients, a prospective cohort study reported that 38% of patients reported PTSD symptoms in questionnaires after abdominal sepsis.[23] PTSD among survivors of sepsis might have also caused the development of sleep disorders in our study, especially considering that disorders, such as insomnia and nightmares, are common in adults with PTSD symptoms.[24] The prevalence of PTSD in sepsis survivors registered in the NHIS database was extremely low at 0.2%; however, considering that PTSD might be accompanied by sleep disorder,[17] many cases of PTSD among sepsis survivors were not captured in the NHIS database in this study.

Similarly, the results regarding sleep disorder with benzodiazepine or Z-drug are interesting. In South Korea, benzodiazepines and Z-drugs are cautiously prescribed by physicians to ensure that sepsis survivors with symptoms of severe sleep disorder continuously take these drugs. Additionally, another cohort study reported that benzodiazepine use was independently associated with a higher risk of mortality;[25] thus, the pharmacologic effect of benzodiazepines might similarly affect the study results. However, information regarding this issue is still lacking, and more research is needed to confirm the relationship between sleep disorder, benzodiazepine or Z-drug use, and long-term survival among sepsis survivors.

Table 4 Sensitivity Analyses of Multivariable Cox Regression Model for 5-Year All-Cause Mortality According to Sleep Disorder with Depression or PTSD and Sleep Disorder with BDZ or Z-Drug Use

Variable	Multivariable Cox Model	*P*-value
	HR (95% CI)	
Sleep disorder before and after sepsis (Model 1)		
Control group (n=34,953)	1	
Pre-sepsis sleep disorder group without PTSD or depression (n=4796)	1.19 (1.13, 1.25)	<0.001
Pre-sepsis sleep disorder group with PTSD or depression (n=3142)	1.21 (1.13, 1.29)	<0.001
Post-sepsis sleep disorder group without PTSD or depression (n=1878)	1.67 (1.56, 1.79)	<0.001
Post-sepsis sleep disorder group with PTSD or depression (n=1057)	2.01 (1.84, 2.19)	<0.001
Sleep disorder before and after sepsis (Model 2)		
Control group (n=34,953)	1	
Pre-sepsis sleep disorder group without BDZ or Z-drug use (n=6409)	1.18 (1.13, 1.23)	<0.001
Pre-sepsis sleep disorder group with BDZ or Z-drug use (n=1529)	1.30 (1.18, 1.43)	<0.001
Post-sepsis sleep disorder group without BDZ or Z-drug use (n=2432)	1.76 (1.66, 1.86)	<0.001
Post-sepsis sleep disorder group with BDZ or Z-drug use (n=503)	2.02 (1.77, 2.30)	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; PTSD, post-traumatic stress disorder; BDZ, benzodiazepine.

The difference in the association of pre- and post-sepsis sleep disorder groups with 5-year all-cause mortality is a notable finding in this study. A previous study reported that sleep disorders are highly comorbid with other critical medical conditions, such as diabetes mellitus, various cardiovascular diseases, respiratory, gastrointestinal, urinary, and neurologic disorders.[26] Therefore, pre-sepsis sleep disorder might reflect the comorbid medical status before sepsis treatment in this study. However, the post-sepsis sleep disorder diagnosis within 1 year after sepsis diagnosis might reflect sequelae from sepsis. As an important pathophysiology of sepsis, it has been reported that brain damage is caused by sepsis due to excessive microglial activation, impaired cerebral perfusion, and blood-brain-barrier dysfunction.[27] Magnetic resonance imaging studies have shown that brain lesions and atrophy were dominant in sepsis patients with worse acute physiology and chronic health evaluation (APACHE) II and sequential organ failure assessment (SOFA) scores.[28] Since sleep disorders were common among patients with neurologic disorders,[29] it is possible that the post-sepsis sleep disorder group has more sequelae than both the control and pre-sepsis sleep disorder groups, and this is attributable to the poorer long-term survival among sepsis survivors.

This study has several limitations. First, as we extracted and analyzed the data retrospectively, the reliability and quality of data might be limited. For example, we cannot guarantee that all sepsis survivors with sleep apnea (G47.3) underwent polysomnography for proper diagnosis in our study. Second, some important physiologic variables, such as body mass index, were not included in the analysis because they were not included in the NHIS database. Third, we used the ICD-10 codes registered in the NHIS database to calculate the Charlson comorbidity indexes of sepsis survivors. However, some of the underlying diseases specified using these ICD-10 codes might not reflect the actual underlying diseases. Fourth, we did not consider the type of sleep disorder such as insomnia and parasomnia. The different types of sleep disorders among sepsis survivors might affect the results of this study. Lastly, we did not include important patient parameters that may reflect the severity of sepsis. For example, the APACHE II and SOFA scores for sepsis patients were not included in our analysis because the NHIS database only provides data regarding the prescribed drugs, procedural information, and registered ICD-10 disease codes. However, we collected the data regarding endotracheal intubation, vasopressor, ventilator support, and CRRT and ECMO use during sepsis treatment to adjust for major organ failure in patients with sepsis.

Conclusions

In conclusion, 6.4% of sepsis survivors in South Korea were newly diagnosed with a sleep disorder within 1 year after

sepsis diagnosis. Although both pre- and post-sepsis sleep disorders were associated with a higher 5-year all-cause mortality rate, the risk of 5-year all-cause mortality in the post-sepsis sleep disorder group was higher than that in the pre-sepsis sleep disorder group. In addition, these association was more evident in the sleep disorder group with PTSD or depression and benzodiazepine or Z-drug user. Our results suggest that sepsis survivors who experience sleep disorder before and after sepsis constituted the high-risk group, towards which interventions may be directed.

Abbreviations

APACHE, acute physiology and chronic health evaluation; CI, confidence interval; CRRT, continuous renal replacement; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th revision; ICU, intensive care units; NHIS, National Health Insurance Service; PTSD, post-traumatic stress disorder; SOFA, sequential organ failure assessment.

Data Sharing Statement

All data will be available upon reasonable request to corresponding author.

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (X-1912-580-902) and the Health Insurance Review and Assessment Service (NHIS-2020-1-095). The requirement for informed consent was waived because the data analyses were performed retrospectively using anonymized data derived from the South Korean NHIS database.

Acknowledgments

In-Ae Song and Hye Yoon Park are co-first authors for this study.

Author Contributions

Tak Kyu Oh designed the study, analysed the data, interpreted the data, and drafted the manuscript; Hye Yoon Park and In-Ae Song contributed to the study conceptualization, acquisition of data, and review of manuscript.; All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare that they have no competing interests.

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