Research Square

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Association of Pre-existing Insomnia with Short- and Long-Term Mortality in Patients with Sepsis Admitted to the Intensive Care Unit: A Retrospective Cohort Study Using MIMIC-IV

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Abstract

PURPOSE

The association between pre-existing insomnia and mortality in ICU patients with sepsis is uncertain. We assessed mortality at 28, 90, and 365 days.

METHODS

Adults meeting an operational Sepsis-3 definition in MIMIC-IV version 3.1 were included. Pre-existing insomnia was identified from diagnoses recorded before the index admission. Associations were estimated using adjusted Cox models, propensity score matching, overlap weighting, and doubly robust models. Sleep-disorder subtypes were examined in exploratory 1:1 matched analyses.

RESULTS

The cohort included 19,609 patients; 403 had pre-existing insomnia and 18,457 had no prior sleep disorder. In the unmatched cohort, adjusted hazard ratios (HRs) for 28-, 90-, and 365-day mortality were 1.24 (95% confidence interval [CI], 1.05–1.48), 1.28 (1.10–1.50), and 1.31 (1.14–1.50). After 1:3 matching, 393 patients with insomnia and 1,179 controls remained. Associations remained for 90-day (HR, 1.19; 95% CI, 1.04–1.36) and 365-day mortality (HR, 1.24; 1.09–1.40), but not for 28-day mortality (HR, 1.13; 0.98–1.32). In exploratory 1:1 matched analyses, 365-day mortality HRs were 1.16 (95% CI, 0.99–1.36; P = 0.073) for insomnia and 1.05 (0.93–1.20; P = 0.420) for sleep apnea.

CONCLUSION

Pre-existing insomnia was associated with higher 90- and 365-day mortality, but the matched 28-day estimate was not statistically significant. These observational findings do not establish causality.

1. Introduction

Sepsis is a life-threatening condition characterized by organ dysfunction resulting from infection. Advances in early recognition, antimicrobial therapy, and organ support have improved survival during the acute phase. Nevertheless, survivors remain at increased risk of death and physical, cognitive, and psychological impairments after hospital discharge [1–3]. Patients with sepsis admitted to the intensive care unit (ICU) often have more severe organ dysfunction and are particularly vulnerable to poor long-term outcomes. Identifying relevant clinical characteristics may help stratify risk and guide follow-up and rehabilitation after discharge.

Pre-existing insomnia warrants attention as a clinically relevant baseline condition. It commonly coexists with anxiety, depression, pain, and metabolic or neurological disorders. It may also be accompanied by dysregulated stress responses and disturbances in inflammatory and immune regulation, potentially affecting the host response to severe infection and recovery after sepsis [4–8]. This study focuses on insomnia that predates ICU admission, distinguishing it from sleep disturbances arising during hospitalization because of critical illness, pain, environmental disruption, or medication use. Whether pre-existing insomnia is associated with 28-day, 90-day, and 365-day mortality in ICU patients with sepsis remains unclear after accounting for comorbidities and acute illness severity.

Previous studies have examined disrupted sleep architecture, reduced sleep duration, and loss of rapid eye movement sleep in critically ill patients. These disturbances were associated with the need for mechanical ventilation, extubation outcomes, and other adverse ICU outcomes [9–12]. A Korean nationwide cohort study of 45,826 sepsis survivors found that sleep disorders occurring before or after sepsis were associated with higher 5-year mortality [1]. Patients with sleep apnea have also been reported to have higher in-hospital mortality when they develop sepsis [13]. However, these studies differed in their populations, sleep-disorder definitions, and outcome windows. Notably, the Korean cohort included only patients who survived at least one year. It also lacked detailed measures of acute illness severity, such as Sequential Organ Failure Assessment (SOFA) or Acute Physiology and Chronic Health Evaluation (APACHE) scores. Whether pre-existing insomnia is associated with 28-day, 90-day, and 365-day mortality in ICU patients with sepsis therefore remains unresolved after adequately accounting for acute illness severity.

Accordingly, we examined the association between pre-existing insomnia and all-cause mortality at 28, 90, and 365 days among ICU patients with sepsis. These time points allowed us to assess whether the association was confined to acute illness or persisted through the first year.

2. Methods

2.1 Data Source and Study Population

This retrospective cohort study used the Medical Information Mart for Intensive Care IV (MIMIC-IV) version 3.1 database, a de-identified critical care database available through PhysioNet [21, 22]. Access to the database requires completion of the required training and authorization. We included adults aged ≥ 18 years and retained the earliest ICU admission for each patient from 2008 onward. Among 94,458 ICU admissions, this yielded 65,366 unique patients. We excluded 6,945 patients whose first hospital service was cardiac surgery, leaving 58,421 patients. We then excluded 13,231 patients whose ICU stay was < 24 h, leaving 45,190 patients. No records were excluded because of missing core analysis variables (n = 0). We then applied the operational Sepsis-3 definition [23], yielding a final cohort of 19,609 ICU patients with sepsis (Fig. 1).

Sepsis was defined using an operational definition based on the Sepsis-3 criteria. Suspected infection was identified from records of antimicrobial administration and microbiological cultures. A culture obtained within 24 h after antimicrobial initiation or antimicrobials initiated within 72 h after culture collection constituted a qualifying combination. The earliest qualifying time was designated as the time of suspected infection. This time had to fall between 48 h before ICU admission and 24 h after ICU admission. Patients with suspected infection and a total SOFA score ≥ 2 during the first 24 h after ICU admission were classified as having sepsis.

Baseline illness severity was assessed using the total SOFA score during the first 24 h after ICU admission. SOFA assesses six organ systems: respiratory, coagulation, liver, cardiovascular, central nervous system, and renal, with each component scored from 0 to 4. Respiratory scores used the lowest PaO_2/FiO_2 ratio and mechanical ventilation status. Coagulation and liver scores used platelet count and bilirubin concentration, respectively. Cardiovascular scores used the lowest mean arterial pressure and vasopressor use. Central nervous system scores used the lowest Glasgow Coma Scale score. Renal scores used the highest creatinine concentration, 24-h urine output, and dialysis status. Missing components were assigned a score of 0 when calculating the total SOFA score.

Pre-existing sleep disorders were identified from diagnoses recorded during hospitalizations before the index admission. Diagnostic codes were standardized using the International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10). A diagnosis was considered pre-existing if its associated hospitalization began before the index admission. Diagnoses recorded during the index admission were excluded from exposure ascertainment, and no fixed look-back period was applied. Overall pre-existing sleep disorders were defined by ICD-9 codes beginning with 307.4, 327, or 780.5, or ICD-10 codes beginning with F51 or G47. The primary exposure, pre-existing insomnia, was defined by ICD-9 codes 307.41, 307.42, 327.00, 327.01, 327.02, 327.09, 780.51, or 780.52, or ICD-10 codes F51.0 or G47.0.

For exploratory subtype analyses, pre-existing sleep apnea was defined by ICD-9 codes 327.2, 780.51, 780.53, or 780.57, or ICD-10 code G47.3. Because ICD-9 code 780.51 was included in both the insomnia and sleep apnea definitions, these subtypes were not mutually exclusive. The 62 patients meeting both definitions were included in both subtype-specific exposed groups. Other sleep disorders were defined as diagnoses meeting the overall sleep-disorder definition but not the criteria for insomnia or sleep apnea. Each subtype was analyzed separately, using patients without any pre-existing sleep disorder as controls.

Follow-up began at ICU admission. The primary outcomes were all-cause mortality within 28, 90, and 365 days. The date of death was obtained preferentially from hospitalization records and, when unavailable, from the recorded date of death. Deaths within each follow-up window were counted as events; patients without an observed death by the end of the window were right-censored at that time.

2.2 Covariates and Data Extraction

Candidate covariates included demographic characteristics (age, sex, race, marital status, insurance type, and language) and hospitalization and ICU characteristics (first ICU unit and hospital service). We also considered pre-existing comorbidities (diabetes, anxiety, depression, dementia, and Parkinson's disease) and early illness severity (SOFA score, mechanical ventilation, vasopressor use, and dialysis). Comorbidities were identified using diagnosis codes and diagnostic names recorded during prior hospitalizations. Relevant demographic, diagnostic, monitoring, laboratory, medication, microbiological, and procedural records were standardized with respect to timing and diagnoses and linked to the index admission. ICU and hospital lengths of stay were used only for descriptive purposes and were excluded from the primary propensity score model.

2.3 Propensity Score Matching and Weighting

Propensity scores were estimated using logistic regression with prespecified demographic, hospitalization and ICU, comorbidity, and illness-severity covariates. The primary insomnia analysis used 1:3 nearest-neighbor propensity score matching (PSM). We used 1:2 matching for sensitivity analysis and 1:1 matching for subtype analyses. All matching was performed without replacement, with a caliper width of 0.2 standard deviations of the logit-transformed propensity score. Weighted analyses used stabilized inverse probability of treatment weighting (IPTW), with propensity scores truncated at the 1st and 99th percentiles. We also used overlap weighting, defining weights as 1 − PS for exposed patients and PS for unexposed patients, where PS denotes the propensity score. An overlap-weighted doubly robust Cox model additionally adjusted for the prespecified covariates. Covariate balance before and after matching or weighting was assessed using standardized mean differences (SMDs). Cox models were fitted with robust standard errors.

2.4 Statistical Analysis

The first eligible ICU admission for each patient was the unit of analysis. Continuous variables were summarized as medians with interquartile ranges (IQRs), and categorical variables as counts and percentages. Between-group comparisons used the Mann–Whitney U test, chi-square test, or Fisher's exact test, as appropriate. Survival was assessed using Kaplan–Meier curves and the log-rank test. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs). We fitted unadjusted, demographically adjusted, and fully adjusted models. For the 1:2 and 1:3 propensity score–matched Cox models, robust standard errors were clustered by matched set using the matched-set identifier (match_pair_id). Weighted models used the corresponding weights, and doubly robust models additionally adjusted for the prespecified covariates. All tests were two-sided, with $P < 0.05$ considered statistically significant. No additional correction for multiple comparisons was applied. Analyses were conducted in Python using the pandas, SciPy, and lifelines packages.

2.5 Sensitivity Analyses

Sensitivity analyses included 1:2 propensity score matching and stabilized inverse probability of treatment weighting (IPTW) without truncation or with two-sided truncation at 0.5%, 1%, 2.5%, 5%, and

10%. All subtype analyses were exploratory. Because covariate imbalance persisted after IPTW, these estimates were interpreted as supportive evidence. No correction for multiple comparisons was applied.

3. Results

3.1 Study Cohort Selection and Baseline Characteristics

We identified 94,458 ICU admissions, of which 65,366 remained after retaining only the first admission for each patient. Excluding patients whose first hospital service was cardiac surgery left 58,421 records; excluding those with ICU stays of < 24 h left 45,190. Applying the operational Sepsis-3 definition yielded a final cohort of 19,609 ICU patients with sepsis (Fig. 1). The primary analysis included 403 patients with pre-existing insomnia and 18,457 without a pre-existing sleep disorder. After 1:3 propensity score matching, 393 patients with pre-existing insomnia and 1,179 controls remained. The absolute SMDs for all covariates were < 0.1 (Table 1 and Fig. 2).

Table 1
Baseline characteristics of patients with pre-existing insomnia and those without a pre-existing sleep disorder after 1:3 propensity score matching (PSM). Data are presented as median (interquartile range) or number (percentage). SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment.

Variable	Pre-existing insomnia (n = 393)	No pre-existing sleep disorder (n = 1179)	SMD
Age, years	66.00 (56.00, 77.00)	65.00 (54.00, 78.00)	0.001
Male	205 (52.2%)	617 (52.3%)	0.003
Race: White	305 (77.6%)	889 (75.4%)	0.052
Race: Black	36 (9.2%)	128 (10.9%)	0.057
Race: Other	52 (13.2%)	162 (13.7%)	0.015
Diabetes	132 (33.6%)	430 (36.5%)	0.060
Anxiety	172 (43.8%)	486 (41.2%)	0.051
Depression	187 (47.6%)	565 (47.9%)	0.007
Dementia	32 (8.1%)	104 (8.8%)	0.024
Parkinson’s disease	9 (2.3%)	23 (2.0%)	0.024
SOFA score	7.00 (4.00, 11.00)	7.00 (4.00, 11.00)	0.018
Mechanical ventilation, day 1	133 (33.8%)	385 (32.7%)	0.025
Vasopressor use, day 1	159 (40.5%)	467 (39.6%)	0.017
Dialysis, day 1	9 (2.3%)	22 (1.9%)	0.030

3.2 Association between Pre-existing Insomnia and Mortality Risk

In the fully adjusted analysis of the unmatched cohort, pre-existing insomnia was associated with higher 28-day, 90-day, and 365-day mortality. The corresponding HRs were 1.24 (95% CI, 1.05–1.48; P = 0.014), 1.28 (95% CI, 1.10–1.50; P = 0.001), and 1.31 (95% CI, 1.14–1.50; P < 0.001). After 1:3 propensity score matching, the associations remained statistically significant for 90-day mortality (HR, 1.19; 95% CI, 1.04–1.36; P = 0.012) and 365-day mortality (HR, 1.24; 95% CI, 1.09–1.40; P < 0.001). The association with 28-day mortality was no longer statistically significant (HR, 1.13; 95% CI, 0.98–1.32; P = 0.100). Detailed results are presented in Table 2 and Fig. 3.

Table 2
Association between pre-existing insomnia and mortality in Cox regression and propensity score–matched analyses. PSM, propensity score matching; HR, hazard ratio; CI, confidence interval.

Model	Outcome	HR (95% CI)	P
Unmatched crude Cox	28-day mortality	1.29 (1.09–1.53)	0.003
Unmatched crude Cox	90-day mortality	1.36 (1.18–1.58)	< 0.001
Unmatched crude Cox	365-day mortality	1.44 (1.26–1.65)	< 0.001
Unmatched multivariable Cox	28-day mortality	1.24 (1.05–1.48)	0.014
Unmatched multivariable Cox	90-day mortality	1.28 (1.10–1.50)	0.001
Unmatched multivariable Cox	365-day mortality	1.31 (1.14–1.50)	< 0.001
1:2 PSM crude Cox	28-day mortality	1.13 (0.97–1.33)	0.126
1:2 PSM crude Cox	90-day mortality	1.19 (1.03–1.38)	0.020
1:2 PSM crude Cox	365-day mortality	1.23 (1.07–1.41)	0.003
1:2 PSM multivariable Cox	28-day mortality	1.12 (0.96–1.31)	0.150
1:2 PSM multivariable Cox	90-day mortality	1.19 (1.03–1.38)	0.018
1:2 PSM multivariable Cox	365-day mortality	1.25 (1.09–1.43)	0.001
1:3 PSM crude Cox	28-day mortality	1.12 (0.96–1.30)	0.166
1:3 PSM crude Cox	90-day mortality	1.16 (1.01–1.34)	0.034
1:3 PSM crude Cox	365-day mortality	1.20 (1.05–1.36)	0.006
1:3 PSM multivariable Cox	28-day mortality	1.13 (0.98–1.32)	0.100
1:3 PSM multivariable Cox	90-day mortality	1.19 (1.04–1.36)	0.012
1:3 PSM multivariable Cox	365-day mortality	1.24 (1.09–1.40)	< 0.001

3.3 Matching and Weighting Sensitivity Analyses

After 1:2 propensity score matching, pre-existing insomnia remained associated with higher 90-day mortality (HR, 1.19; 95% CI, 1.03–1.38; P = 0.018) and 365-day mortality (HR, 1.25; 95% CI, 1.09–1.43; P = 0.001). The association with 28-day mortality was not statistically significant (HR, 1.12; 95% CI, 0.96–1.31; P = 0.150). After overlap weighting, the maximum absolute SMD was 0.004. The HRs for 90-day and 365-day mortality were 1.15 (95% CI, 1.03–1.28; P = 0.012) and 1.19 (95% CI, 1.07–1.32; P = 0.001), respectively. The HR for 28-day mortality was 1.11 (95% CI, 0.99–1.23; P = 0.077). The doubly robust model yielded similar results (P = 0.010 for 90-day mortality and P < 0.001 for 365-day mortality). Stabilized IPTW indicated higher 90-day and 365-day mortality risks, but the maximum absolute SMD remained 0.519. These findings were therefore considered supportive sensitivity evidence only. Detailed results are presented in Table 3 and Fig. 4.

Table 3
Sensitivity analyses using weighting methods. IPTW results are presented as supportive evidence because residual covariate imbalance persisted after weighting. IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; SMD, standardized mean difference.

Method	Outcome	HR (95% CI)	P	Balance
Overlap weighting Cox	28-day mortality	1.11 (0.99–1.23)	0.077	Max SMD = 0.004
Overlap weighting Cox	90-day mortality	1.15 (1.03–1.28)	0.012	Max SMD = 0.004
Overlap weighting Cox	365-day mortality	1.19 (1.07–1.32)	0.001	Max SMD = 0.004
Overlap weighting doubly robust Cox	28-day mortality	1.11 (0.99–1.24)	0.070	Max SMD = 0.004
Overlap weighting doubly robust Cox	90-day mortality	1.15 (1.03–1.28)	0.010	Max SMD = 0.004
Overlap weighting doubly robust Cox	365-day mortality	1.19 (1.07–1.32)	< 0.001	Max SMD = 0.004
Stabilized IPTW, 1% trimming	28-day mortality	1.17 (0.96, 1.42)	0.119	Max SMD = 0.519
Stabilized IPTW, 1% trimming	90-day mortality	1.23 (1.02, 1.49)	0.031	Max SMD = 0.519
Stabilized IPTW, 1% trimming	365-day mortality	1.39 (1.17, 1.65)	< 0.001	Max SMD = 0.519

3.4 Sleep-Disorder Subtype Analyses

Exploratory analyses by sleep-disorder subtype used 1:1 propensity score matching. The insomnia analysis included 403 matched pairs, with a maximum absolute SMD of 0.142. Pre-existing insomnia

showed a trend toward higher 365-day mortality, although the association was not statistically significant (HR, 1.16; 95% CI, 0.99–1.36; P = 0.073). The sleep apnea analysis included 800 matched pairs, with a maximum absolute SMD of 0.089. Sleep apnea was not significantly associated with 365-day mortality (HR, 1.05; 95% CI, 0.93–1.20; P = 0.420). Results are presented in Table 4 and Supplementary Fig. S1.

Table 4
Exploratory analyses of sleep-disorder subtypes and 365-day mortality after 1:1 propensity score matching (PSM). These results were not used as the primary evidence. HR, hazard ratio; CI, confidence interval; SMD, standardized mean difference.

Subtype	Exposed, n	Controls, n	Matched pairs, n	Max SMD after PSM	365-day HR (95% CI)	P
Pre-existing insomnia	403	18457	403	0.142	1.16 (0.99, 1.36)	0.073
Pre-existing sleep apnea	801	18457	800	0.089	1.05 (0.93, 1.20)	0.420

4. Discussion

Using MIMIC-IV version 3.1, we found that pre-existing insomnia was associated with higher 90-day and 365-day mortality among ICU patients with sepsis. The association persisted across adjusted Cox models, propensity score matching, overlap weighting, and doubly robust analyses, whereas the 28-day association was not statistically significant after matching.

Our findings are consistent with previous studies linking sleep disorders to higher mortality [1, 7, 8, 13]. However, differences in the sleep conditions examined, patient populations, and follow-up periods limit direct comparisons. The Korean cohort suggested that sleep disorders occurring before or after sepsis were associated with long-term mortality [1]. Our study extends this evidence by examining patients from ICU admission and accounting for acute illness severity, including the SOFA score. After matching, the association was evident at longer-term follow-up but was not statistically significant over the short term. This pattern may reflect the greater influence of acute organ dysfunction and early treatment response on short-term mortality. The potential effects of pre-existing insomnia may become more apparent during recovery and after hospital discharge. Differences in study populations, sleep-disorder definitions, and confounder adjustment warrant caution when interpreting these findings.

Potential mechanisms may involve dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, sympathetic activity, and immune-inflammatory regulation. Coexisting factors may include anxiety and depression, susceptibility to delirium, delayed rehabilitation, and sedative-hypnotic medication use [4–6, 10, 12, 15–20]. However, this study did not measure inflammatory mediators, neuroendocrine activity, objective sleep parameters, or recovery trajectories. These mechanisms therefore remain hypotheses consistent with the findings, rather than established causal pathways.

Pre-existing insomnia may be an often-overlooked aspect of clinical history relevant to long-term risk assessment in ICU patients with sepsis. Clinicians could assess sleep history at ICU admission or hospital discharge and consider psychological status, functional status, and medication use when planning follow-up. However, these observational findings cannot establish that treating insomnia reduces mortality. The benefits of specific interventions should be evaluated in prospective trials [3, 9–12, 20].

This study has several strengths. We used the large MIMIC-IV database, which includes long-term outcome data, and ascertained sepsis cases using an operational definition based on Sepsis-3. Exposure ascertainment was restricted to diagnoses recorded before the index admission, and mortality was assessed across multiple follow-up windows. Matching, weighting, and doubly robust methods allowed us to examine the robustness of the findings.

Several limitations warrant consideration. First, the retrospective design and single-center database limit causal inference and external validity. Second, identifying sleep disorders and insomnia from diagnostic codes introduces the possibility of underdiagnosis and misclassification. Information on insomnia severity and duration, outpatient diagnoses, and objective sleep monitoring was unavailable. Unmeasured factors, including socioeconomic status, lifestyle, post-discharge care, and treatment adherence, may also contribute to residual confounding. Some covariate imbalance remained after matching in the subtype analyses, and substantial imbalance persisted after IPTW. These estimates therefore require cautious interpretation. Assigning a score of 0 to missing SOFA components may also have affected the assessment of illness severity. Clinical subgroup effects specific to pre-existing insomnia were not evaluated, so heterogeneity across patient subgroups remains unknown. Finally, the findings may not be directly generalizable to general-ward patients or populations without sepsis.

5. Conclusion

The association at 90 and 365 days, but not clearly at 28 days, suggests that pre-existing insomnia may mark vulnerability beyond the acute phase of sepsis. It may help identify patients who warrant closer follow-up after discharge. However, its added prognostic value and whether treating insomnia improves outcomes remain to be established.

Declarations

Declaration of competing interests

The authors declare that they have no competing interests.

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Author Contribution

M.W. contributed to data curation and writing – original draft. H.W. contributed to data curation and software. Z.L. contributed to project administration. J.Z. contributed to conceptualization, methodology, supervision, and project administration.

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Data Availability

The data analyzed in this study were obtained from the MIMIC-IV database, available to credentialed researchers through PhysioNet at https://physionet.org/content/mimiciv/. Access requires completion of human subjects research training and a signed data use agreement.

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Figures

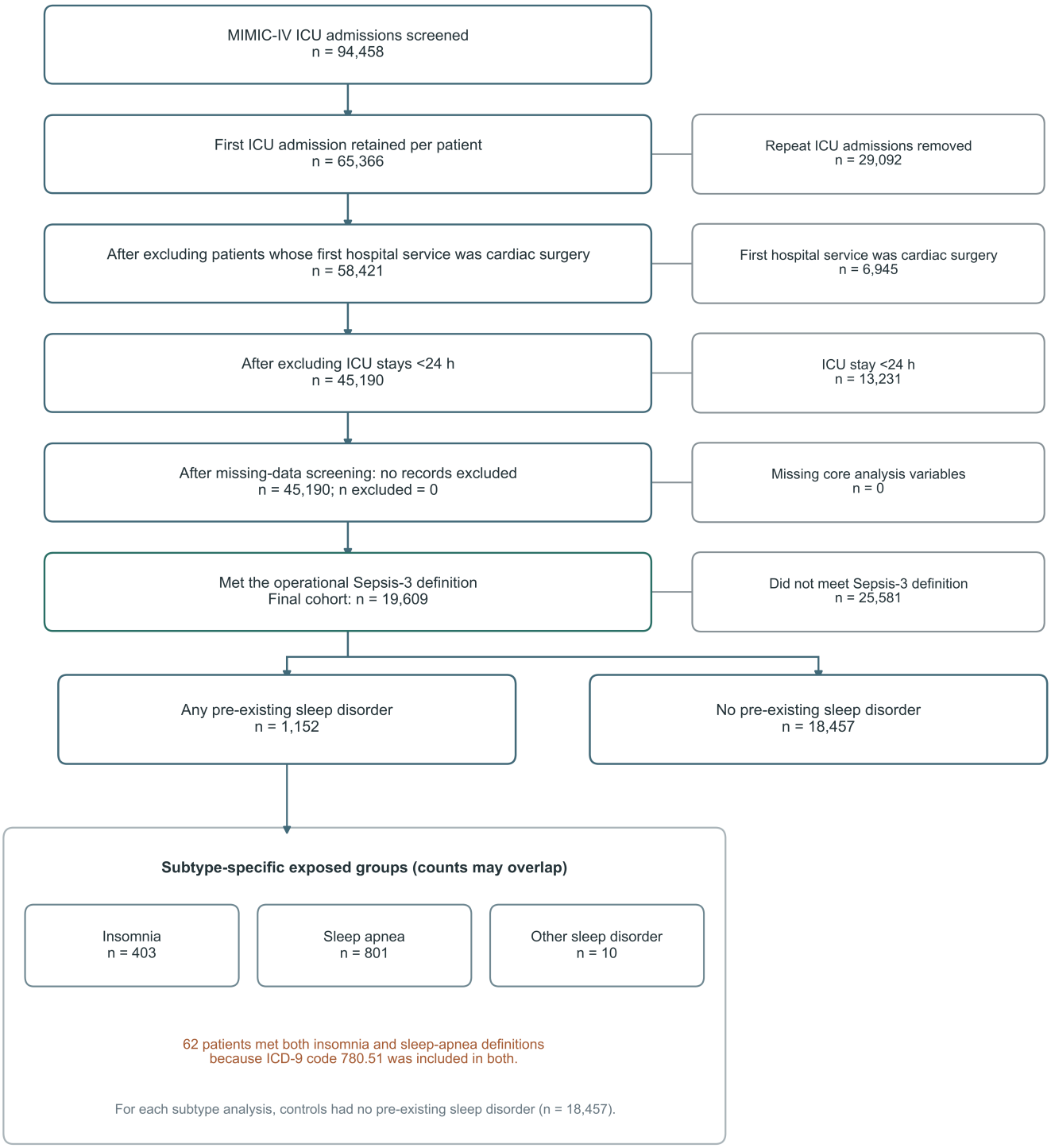


Figure 1

Cohort selection and classification of pre-existing sleep disorders. Subtype counts were not mutually exclusive: 62 patients met both insomnia and sleep-apnea definitions because ICD-9 code 780.51 was included in both. Each subtype analysis used patients without pre-existing sleep disorders (n = 18,457) as controls

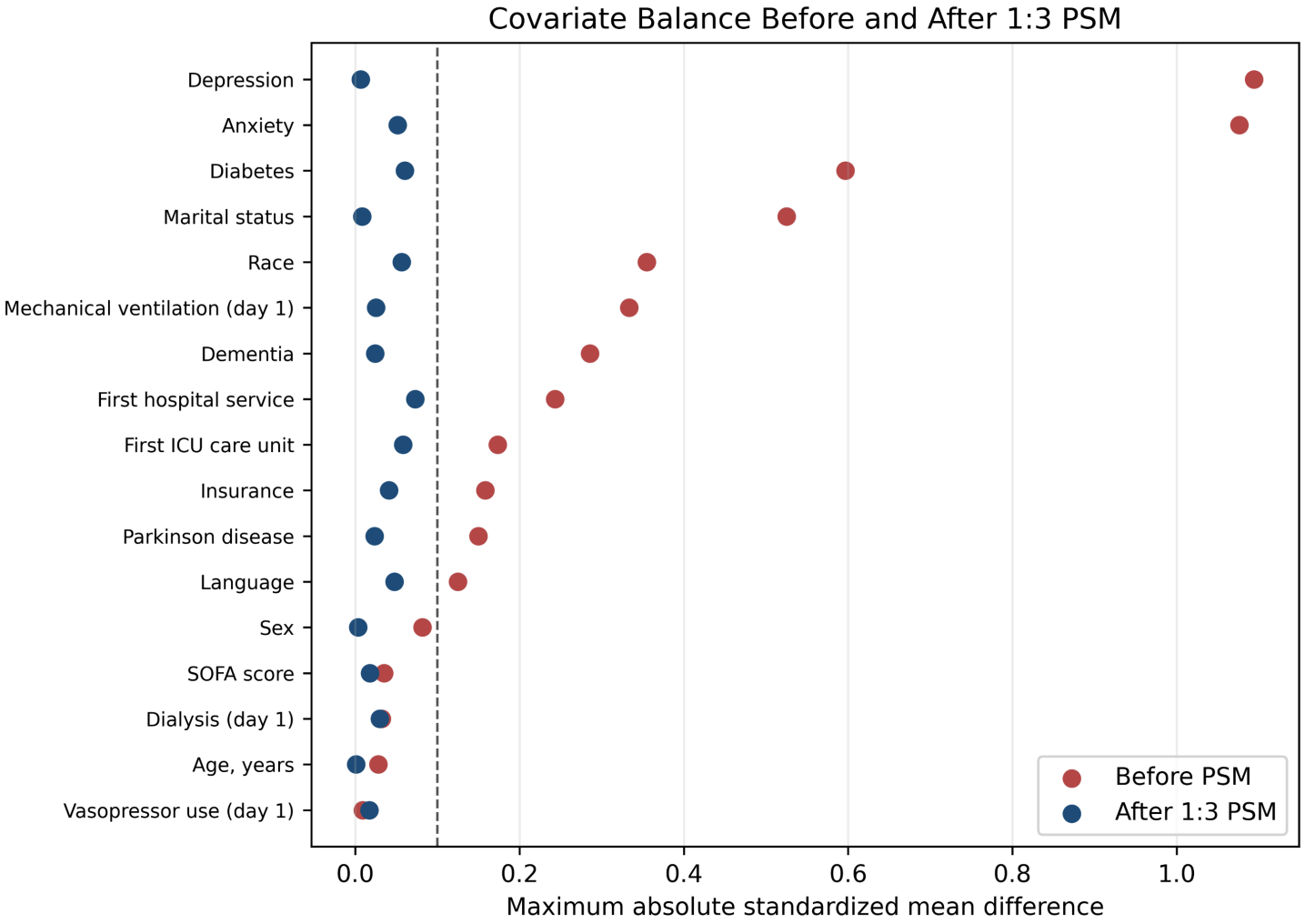


Figure 2

Covariate balance before and after 1:3 propensity score matching (PSM). ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment

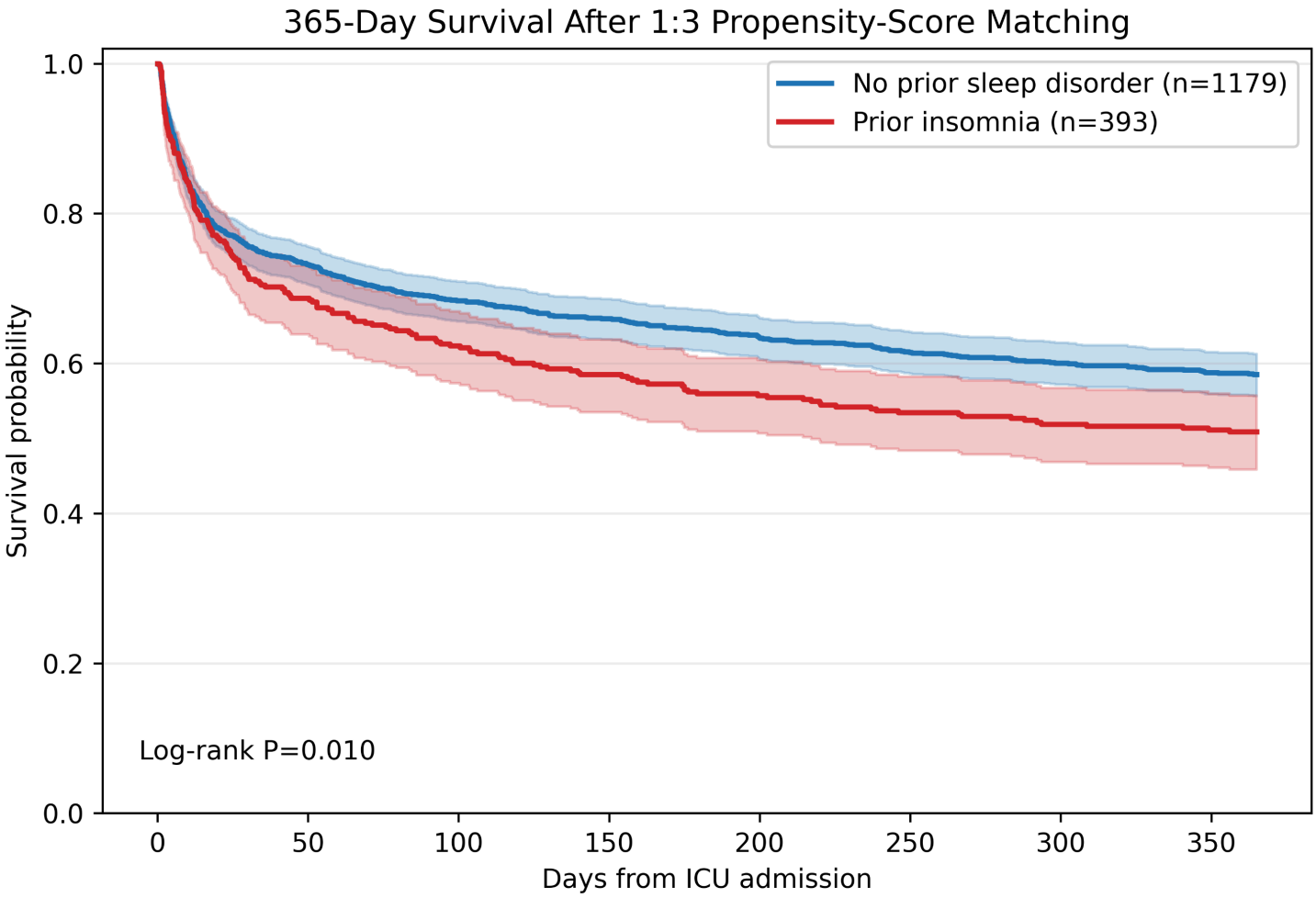


Figure 3

Kaplan–Meier survival curve over 365 days after 1:3 propensity score matching (PSM). ICU, intensive care unit

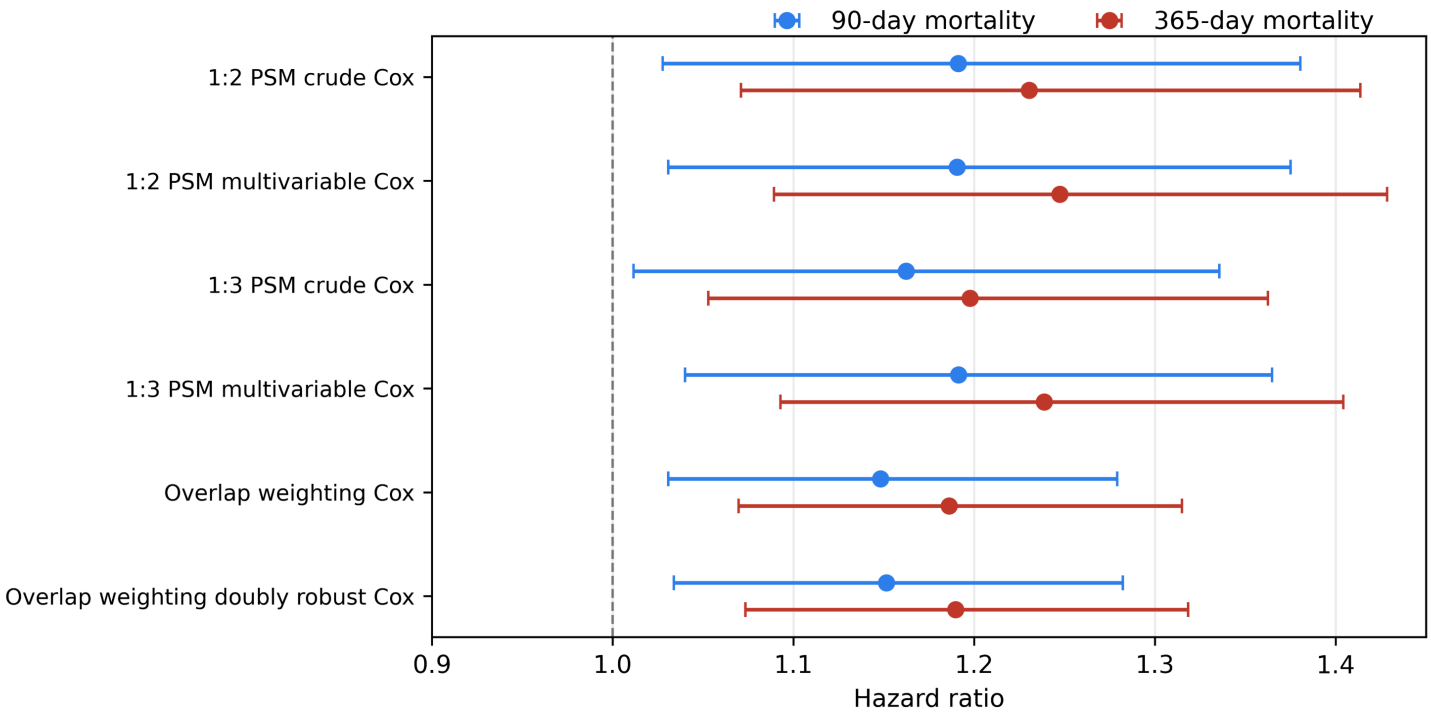


Figure 4

Sensitivity analyses of 90-day and 365-day mortality using matching and weighting. PSM, propensity score matching

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigureS1.pdf