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# Ramelteon exposure and survival of critically Ill sepsis patients: a retrospective study from MIMIC-IV

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## Abstract

**Background** The effect of ramelteon, a melatonin receptor agonist, on survival in septic patients remains unknown. The purpose of this retrospective cohort study was to explore the relationship between ramelteon exposure and survival outcomes in septic patients.

**Methods** Data from septic patients admitted to the intensive care unit (ICU) were extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, with patients categorized into ramelteon exposure and non-exposure groups based on the use of ramelteon. The primary outcome was 30-day mortality, and secondary outcomes included 90-day mortality, in-hospital mortality, length of ICU stay, and hospital stay. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were employed to address confounding variables. Kaplan–Meier (K-M) analysis and Cox proportional hazards regression models for stepwise regression were utilized to assess the impact of ramelteon exposure on survival.

**Results** This study included 22,152 unexposed patients and 2,708 exposed patients, resulting in 2,607 matched pairs after PSM. Following PSM, ramelteon exposure was associated with significantly lower in-hospital mortality (11.6% vs.19.7%, $p < 0.001$), 30-day mortality (13.4% vs. 23.2%, $p < 0.001$), and 90-day mortality (22.1% vs. 30%, $p < 0.001$).K-M curves demonstrated a significant difference in 30-day and 90-day mortality between the two groups ($P < 0.001$), irrespective of PSM application. Both PSM (hazard ratio [HR] = 0.53, 95% confidence intervals [CIs] 0.47–0.61, $p < 0.001$) and IPTW models (HR = 0.59, 95% CI 0.50–0.70, $p < 0.001$) indicated a significant positive effect of ramelteon usage on 30-day mortality among septic patients compared to the non-exposure group.

**Conclusions** This exploratory, retrospective study suggests an association between ramelteon exposure and reduced 30-day and 90-day mortality in septic patients compared with the non-exposure group. Considering the limitations of the retrospective design and the potential for unmeasured confounding, well-designed prospective studies and randomized controlled trials will be needed to confirm these findings.

**Keywords** Ramelteon, Mortality, Melatonin, Sepsis, ICU, MIMIC-IV

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## Introduction

Sepsis is a syndrome characterized by physiological, pathological, and metabolic abnormalities resulting from infection [1]. As a significant global health concern, sepsis is correlated with higher mortality, extended hospital stays, diminished quality of life, and increased healthcare expenditures [2]. In 2017, septic patients accounted for 19.7% of global deaths, posing a substantial challenge to the healthcare system [2]. In North America and Europe, the overall 30-day sepsis death rate was 24.4%, with a 90-day sepsis death rate of 32.2% [3], while in China, the 30-day and 90-day sepsis death rates were 29% and 33.5%, respectively [4]. In addition, sepsis stands as the primary cause of death in intensive care unit (ICU) patients, with a mortality rate exceeding 30% [5].

Ramelteon, an agonist of melatonin receptors (MTs), has been recommended by the American Academy of Sleep Medicine for treating sleep onset insomnia at an 8 mg dosage [6]. Melatonin and ramelteon may serve as interventions to enhance sleep and circadian regulation in ICU, thereby mitigating the incidence of delirium [7]. Ramelteon was associated with a lower risk of delirium (3% vs. 32%) [8]. Notably, it is now understood that ramelteon exhibits six-fold and three-fold greater affinity for MT1 and MT2 receptors than melatonin [9]. Additionally, its half-life is longer than that of melatonin when administered orally (1.36 h vs. 0.75 h) [10, 11]. According to the latest international consensus, sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection [1]. Melatonin and its analogs may contribute to combatting pathogenic bacterial infections [12] and protecting against organ dysfunction during sepsis [13]. The sepsis process is closely tied to inflammation and oxidative stress, with evidence from preclinical studies suggesting that ramelteon can significantly inhibit lipopolysaccharide (LPS)-induced inflammatory response and oxidative stress, thus playing a crucial organ-protective role [14–16].

While a retrospective study found an association between melatonin exposure and reduced in-hospital and 30-day mortality among US veterans with sepsis [17]. A preclinical investigation indicated that ramelteon improved survival in septic animals [18], and ramelteon tended to reduce the length of ICU stay [19].There is a lack of large-scale clinical research exploring the relationship between ramelteon exposure and survival in critically ill patients with sepsis. To address this gap, we hypothesized that ramelteon exposure reduces 30-day and 90-day mortality in sepsis patients. Consequently, this exploratory retrospective cohort study was conducted to investigate the relationship between ramelteon exposure and short-term survival outcomes in critically ill patients with sepsis.

## Methods

### Data source and ethics statement

The retrospective cohort analysis utilized the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (version 3.0, issued July 23, 2024), the latest 3.0 version includes 94,458 patients who were admitted to the ICU. Authorization for this investigation was granted by the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) institutional review boards, with informed consent waived. Database access was granted to a researcher (HYY) who completed the Collaborative Institutional Training Initiative test (name ID: 10,112,186, record ID: 42,408,105). This manuscript adhered to the relevant STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

### Study population

The present study included all patients meeting the diagnostic criteria for sepsis-3 [1]. Inclusion criteria comprised documented or presumed infection and a total sequential organ failure assessment (SOFA) score $\geq 2$ points within 24 h. The exclusion criteria were established as follows: (1) age $< 18$ years, (2) not the first hospitalization and ICU admission, (3) length of ICU stay $< 24$ h, (4) death occurring within 24 h of admission, (5) usage of melatonin analogues other than ramelteon, and (6) the time from ICU admission to the first use of ramelteon was less than the survival time.

### Variable extraction

Data were extracted via a structure query language with Navicat Premium Lite (version 17). The extracted information encompassed various categories, including demographic parameters such as age, gender, race, height, and weight. Additionally, vital signs averaged over the initial 24 h were collected, encompassing heart rate, mean blood pressure, respiratory rate, temperature, saturation of pulse oximetry, glucose, and urine output. The data compilation further involved capturing details on the source of infection and maximum laboratory data, which includes hematocrit, hemoglobin, platelet count, white blood cell (WBC) count, anion gap, bicarbonate, blood urea nitrogen (BUN), creatinine, calcium, sodium, and potassium. Furthermore, information on co-morbidities affecting the survival of septic patients, such as delirium, sleep disorder, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, diabetes, renal disease, malignant cancer, and severe liver disease, was also extracted. In addition to these aspects, severity scores and clinical interventions were documented, covering the SOFA score, Simplified Acute Physiology Score II

(SAPS II), Charlson comorbidity index, invasive mechanical ventilation (IMV), antibiotic usage, continuous renal replacement therapy (CRRT), and use of sedatives, neuromuscular blocking agents, and vasoactive agents.

### Exposure and outcome

The exposure variable centered around the administration of ramelteon during hospitalization. Patients who received ramelteon, whether orally or through a gastric tube, constituted the ramelteon exposure group. Those who did not receive ramelteon were categorized as the non-exposure group.

The primary outcome under consideration was 30-day mortality, with the secondary outcomes encompassing 90-day mortality, in-hospital mortality, the duration of stay in the ICU, and the length of hospital stay. The criteria for these outcomes involved assessing whether a patient passed away within 30 or 90 days after hospital admission, whether the death occurred during the ongoing hospital stay, and the quantification of the current hospital and ICU stay lengths.

### Statistical analysis

In the early stages, R software (version 4.4.1) was employed for preliminary data collection, with multiple imputations utilized to address missing data [20] (if the missing data percentage was less than 40%). Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables were presented as frequencies (n, %). Group comparisons for categorical variables used the Chi-square test or Fisher's exact test, and for continuous variables, the t-test or Mann–Whitney test was applied, as appropriate.

To address confounding factors and enhance result reliability, 1:1 propensity score matching (PSM) with a caliper of 0.02 and propensity score-based inverse probability of treatment weighting (IPTW) was employed. The effectiveness of PSM in minimizing group differences was evaluated using the standardized mean difference (SMD), considering a variable unbalanced if SMD exceeded 0.1 [21]. Before and after PSM, survival analysis for patients exposed and unexposed to ramelteon was conducted using Kaplan–Meier (K-M) analysis and the log-rank test. To explore the relationship between ramelteon exposure and 30-day mortality, univariate and stepwise regression multivariable Cox proportional hazards regression models were employed in PSM cohort. The multivariable Cox regression included five models, each correcting for different factors: Model 1 was corrected for demographic parameters. Model 2 builds upon Model 1 by incorporating the average values of vital signs recorded during the initial 24 h. Model 3 enhances Model 2 by including the source of infection and the maximum values of laboratory data. Model 4 extends Model 3 by adding combined disease comorbidities, while Model 5 further develops Model 4 by incorporating severity scores and clinical interventions.

Following PSM, subgroup analyses were conducted to evaluate whether the association between ramelteon exposure and 30-day mortality varied according to various factors, including age, SOFA score, charlson comorbidity index, delirium, vasoactive agent usage, neuromuscular blocking agents usage, sedatives usage, CRRT and IMV. Sensitivity analyses were conducted on individuals with various organ disorders.

Finally, the lengths of both ICU and hospital stays were included as covariates for PSM to investigate how time-related outcome indicators affect 30-day mortality. Additionally, restricted cubic splines were plotted to explore the association between the duration of ramelteon exposure and the risk of 30-day mortality.The results were presented as hazard ratios (HR) with 95% confidence intervals (CIs). A significance threshold of $p$-value < 0.05 was adopted for determining statistical significance.

## Results

In the MIMIC-IV database, a total of 41,296 individuals were diagnosed with sepsis, and after applying the eligibility criteria, 24,860 individuals were included. Among these, 22,152 were in the ramelteon non-exposure group, and 2,708 were in the ramelteon exposure group (Fig. 1). Baseline characteristics, as presented in Table 1, indicated that the ramelteon exposure cohort was characterized by older age (median [IQR] = 69.0 [59.0, 79.0] years vs. 68.0 [56.0, 79.0] years), a higher proportion of male patients (62.1% vs 57.8%), and a lower proportion of white patients (62% vs 65.6%) compared to the non-exposure group. In the ramelteon exposure group, all patients received 8 mg of ramelteon orally or through a gastric tube, with a median frequency of 8 times.Missing data for covariates, including height, weight, vital signs, and laboratory data, varied but accounted for less than 25% of the total (Fig. S1). After 1:1 PSM, 2,607 ramelteon unexposed patients and 2,607 ramelteon exposed patients were successfully matched, and Fig.S2 shows that the characteristics of the two groups were well matched.Clinical outcomes, outlined in Table 1, initially suggested lower in-hospital mortality (16.1% vs. 11.9%), 30-day mortality (19.2% vs. 13.9%), and 90-day mortality (25.2% vs. 22.6%) in ramelteon exposed patients compared to unexposed patients. The exposure group exhibited longer ICU and hospital stays. After PSM, the association between ramelteon and lower mortality persisted, remaining significant for in-hospital mortality (19.7% vs. 11.6%, $p$ < 0.001), 30-day mortality (23.2% vs.

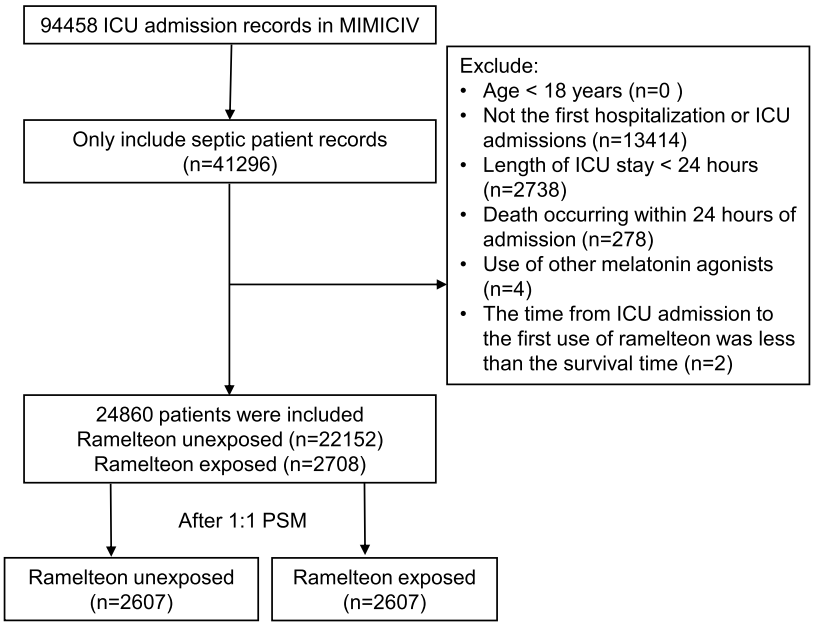


**Fig. 1** Flow chart of patient selection

13.4%, $p<0.001$), and 90-day mortality (30.0% vs. 22.1%, $p<0.001$). Additionally, the exposure group was associated with longer lengths of ICU stay (median [IQR] = 5.1 [2.6, 11.0] days vs. 4.1 [2.2, 8.6] days) and hospital stay (median [IQR] = 16.8 [9.6, 28.8]days vs. 10.5 [6.3, 18.6] days). Kaplan–Meier curves consistently indicated a significant difference in both 30-day and 90-day mortality ($P<0.001$, Fig. 2A and B), regardless of PSM ($P<0.001$, Fig. 2C and D) and IPTW ($P<0.001$, Fig. 2E and F).

In the univariate Cox proportional hazards model, ramelteon exposure was associated with significantly lower 30-day mortality (unadjusted HR = 0.66, 95% CI (0.60–0.74), $P<0.001$). The association between ramelteon and lower 30-day mortality persisted in both the PSM (HR = 0.53, 95% CI (0.47–0.60), $P<0.001$) and IPTW (HR = 0.59, 95% CI (0.50–0.70), $P<0.001$) models. And in a comprehensive multivariable Cox model, the hazard ratio for different corrected covariates consistently favored the exposure group in five models (HR = 0.529, 0.525, 0.531, 0.525 and 0.528, respectively). More details are provided in Table 2 and Table S1-S5.

The results of the subgroup analyses concerning 30-day mortality are illustrated in Fig. 3. A significant association was observed between 30-day mortality and all subgroups ($P<0.05$), except for patients who did not receive propofol. Additionally, a significant interaction effect was identified in three subgroups: age, neuromuscular blocking agents, sedatives exposure and IMV.

Sensitivity analysis demonstrated that ramelteon exposure significantly reduced the risk of death at 30 days in septic patients with organ dysfunction of respiration (HR = 0.56, 95% CI 0.44–0.70, $p<0.001$), liver (HR = 0.57, 95% CI 0.43–0.75, $p<0.001$),coagulation (HR = 0.56, 95% CI 0.44–0.70, $p<0.001$),cardiovascular(HR = 0.50, 95% CI 0.42–0.59, $p<0.001$), central nervous system (HR = 0.65, 95% CI 0.52–0.81, $p<0.001$), and renal (HR = 0.62, 95% CI 0.52–0.74, $p<0.001$). More details are provided in Fig. 4.

Finally, to examine the effect of hospital and ICU stay lengths on mortality outcomes, propensity score matching (PSM) was re-performed with these lengths included as covariates(Fig. S3). The $p$-value from the log-rank test continued to support the stability of the results(Fig. S3). Additionally, restricted cubic splines illustrating a decrease in the risk of 30-day mortality with increasing duration of ramelteon exposure, displaying a roughly inverted "S" relationship(Fig. S4).

## Discussion

In this exploratory cohort study, a total of 24,860 adult patients diagnosed with sepsis from the MIMIC-IV database were included. Within the 30-day period, 366 patients in the ramelteon exposure group and 4,246 in the non-exposure group experienced mortality (13.5% vs. 19.2%). After employing PSM to mitigate potential confounders, ramelteon exposure was associated with a reduction in 30-day mortality. The results from multivariable Cox regression analysis, subgroup analysis, and sensitivity analysis collectively supported the robustness of this conclusion. Additionally, ramelteon

**Table 1** Baseline characteristics and clinical outcomes between the two groups before and after PSM

| Characteristic | Before PSM | | | | After PSM | | | |
|---|---|---|---|---|---|---|---|---|
| | **Overall** *N* = 24,860 | **Ramelteon unexposed** *N* = 22,152 | **Ramelteon exposed** *N* = 2,708 | **SMD** | **Overall** *N* = 5,214 | **Ramelteon unexposed** *N* = 2,607 | **Ramelteon exposed** *N* = 2,607 | **SMD** |
| **Demographic parameters** | | | | | | | | |
| Gender(male), n (%) | 14,492.0 (58.3%) | 12,811.0 (57.8%) | 1,681.0 (62.1%) | 0.09 | 3,215.0 (61.7%) | 1,604.0 (61.5%) | 1,611.0 (61.8%) | 0.01 |
| Race(white), n (%) | 16,220.0 (65.2%) | 14,541.0 (65.6%) | 1,679.0 (62.0%) | 0.08 | 3,279.0 (62.9%) | 1,661.0 (63.7%) | 1,618.0 (62.1%) | 0.03 |
| Age (years), Median (Q1, Q3) | 68.0 (57.0, 79.0) | 68.0 (56.0, 79.0) | 69.0 (59.0, 79.0) | 0.07 | 69.0 (58.0, 79.0) | 69.0 (58.0, 80.0) | 69.0 (58.0, 79.0) | 0.01 |
| Height(cm), Median (Q1, Q3) | 170.0 (162.6, 178.0) | 170.0 (161.3, 178.0) | 170.0 (163.0, 178.0) | 0.06 | 170.0 (163.0, 178.0) | 170.0 (163.0, 178.0) | 170.0 (163.0, 178.0) | 0.02 |
| Weight(kg), Median (Q1, Q3) | 80.0 (67.3, 95.7) | 80.0 (67.2, 95.5) | 80.9 (68.0, 96.9) | 0.04 | 80.2 (67.3, 96.2) | 80.0 (66.8, 96.0) | 80.8 (68.0, 96.5) | 0.04 |
| **Vital signs** | | | | | | | | |
| Heart rate(bpm), Median (Q1, Q3) | 85.1 (75.4, 97.0) | 85.2 (75.5, 97.0) | 84.8 (74.5, 97.7) | 0.00 | 84.8 (75.0, 97.6) | 84.7 (75.3, 97.7) | 84.8 (74.6, 97.5) | < 0.01 |
| MBP (mmHg), Median (Q1, Q3) | 75.7 (70.4, 82.4) | 75.5 (70.2, 82.2) | 77.1 (71.9, 84.0) | 0.19 | 77.1 (71.7, 84.0) | 77.2 (71.5, 84.3) | 77.1 (71.8, 83.9) | 0.01 |
| Respiratory rate(bpm), Median (Q1, Q3) | 19.0 (16.8, 22.1) | 18.9 (16.7, 22.0) | 19.8 (17.5, 22.8) | 0.19 | 19.7 (17.4, 22.8) | 19.7 (17.3, 23.0) | 19.8 (17.4, 22.7) | 0.01 |
| Temperature(℃), Median (Q1, Q3) | 36.9 (36.6, 37.2) | 36.9 (36.6, 37.2) | 36.9 (36.7, 37.2) | 0.09 | 36.9 (36.6, 37.2) | 36.9 (36.6, 37.2) | 36.9 (36.7, 37.2) | 0.03 |
| $SPO_2$(%), Median (Q1, Q3) | 97.3 (95.8, 98.5) | 97.3 (95.9, 98.6) | 96.8 (95.3, 98.3) | 0.19 | 96.9 (95.3, 98.3) | 96.9 (95.3, 98.3) | 96.8 (95.3, 98.3) | 0.03 |
| Glucose(mg/dl), Median (Q1, Q3) | 132.0 (114.8, 160.5) | 131.8 (114.8, 159.7) | 133.9 (114.0, 165.7) | 0.03 | 133.3 (114.0, 167.3) | 133.2 (114.0, 169.4) | 133.7 (113.6, 165.3) | < 0.01 |
| Urine output(ml), Median (Q1, Q3) | 1,545.0 (935.0, 2,350.0) | 1,560.0 (950.0, 2,368.0) | 1,375.0 (800.0, 2,180.0) | 0.12 | 1,372.5 (800.0, 2,170.0) | 1,365.0 (800.0, 2,160.0) | 1,375.0 (800.0, 2,175.0) | 0.01 |
| **Laboratory** | | | | | | | | |
| Hemoglobin(g/dl), Median (Q1, Q3) | 10.9 (9.3, 12.6) | 10.9 (9.3, 12.6) | 11.1 (9.2, 12.9) | 0.05 | 11.1 (9.3, 12.8) | 11.1 (9.4, 12.7) | 11.1 (9.2, 12.8) | 0.01 |
| Hematocrit (%), Median (Q1, Q3) | 33.3 (28.4, 38.0) | 33.2 (28.4, 37.9) | 34.4 (28.8, 39.4) | 0.15 | 34.3 (29.0, 39.1) | 34.2 (29.4, 38.9) | 34.4 (28.7, 39.3) | 0.02 |
| WBC ($\times 10^9$), Median (Q1, Q3) | 10.8 (7.5, 15.3) | 10.8 (7.5, 15.3) | 10.8 (7.8, 15.5) | 0.06 | 10.9 (7.7, 15.5) | 10.9 (7.6, 15.6) | 10.8 (7.8, 15.4) | 0.03 |
| Platelet ($\times 10^{12}$), Median (Q1, Q3) | 190.0 (135.0, 256.0) | 189.0 (134.0, 255.0) | 199.0 (143.0, 266.0) | 0.10 | 196.0 (141.0, 264.0) | 194.0 (137.0, 263.0) | 197.0 (143.0, 265.0) | 0.01 |
| BUN (mg/dl), Median (Q1, Q3) | 20.0 (14.0, 34.0) | 20.0 (14.0, 33.0) | 22.0 (15.0, 37.0) | 0.09 | 22.0 (15.0, 37.0) | 22.0 (15.0, 37.0) | 22.0 (15.0, 37.0) | 0.01 |
| Creatinine(mg/dl), Median (Q1, Q3) | 1.0 (0.8, 1.6) | 1.0 (0.8, 1.5) | 1.1 (0.8, 1.7) | 0.11 | 1.1 (0.8, 1.7) | 1.1 (0.8, 1.7) | 1.1 (0.8, 1.7) | 0.01 |
| Sodium(mmol/L), Median (Q1, Q3) | 139.0 (136.0, 141.0) | 139.0 (136.0, 141.0) | 138.0 (135.0, 141.0) | 0.10 | 138.0 (135.0, 141.0) | 138.0 (135.0, 141.0) | 138.0 (135.0, 141.0) | 0.03 |
| Potassium(mmol/L), Median (Q1, Q3) | 4.1 (3.8, 4.6) | 4.1 (3.7, 4.6) | 4.2 (3.8, 4.7) | 0.15 | 4.2 (3.8, 4.7) | 4.2 (3.8, 4.7) | 4.2 (3.8, 4.7) | 0.01 |
| Calcium(mg/dl), Median (Q1, Q3) | 8.5 (7.9, 9.0) | 8.4 (7.9, 8.9) | 8.5 (8.0, 9.0) | 0.14 | 8.5 (7.9, 9.0) | 8.4 (7.9, 8.9) | 8.5 (8.0, 9.0) | 0.14 |
| Anion gap(mmol/L), Median (Q1, Q3) | 14.0 (12.0, 17.0) | 14.0 (12.0, 17.0) | 14.0 (11.0, 16.0) | 0.16 | 14.0 (11.0, 17.0) | 14.0 (12.0, 17.0) | 14.0 (11.0, 16.0) | 0.02 |
| Bicarbonate(mmol/L), Median (Q1, Q3) | 23.0 (20.0, 26.0) | 23.0 (20.0, 26.0) | 22.0 (19.0, 25.0) | 0.14 | 22.0 (19.0, 25.0) | 22.0 (19.0, 25.0) | 22.0 (19.0, 25.0) | < 0.01 |
| Source of infection, n (%) | | | | 0.47 | | | | 0.04 |
| Blood | 10,651.0 (42.8%) | 9,271.0 (41.9%) | 1,380.0 (51.0%) | | 2,693.0 (51.6%) | 1,366.0 (52.4%) | 1,327.0 (50.9%) | |
| Others/Uncertain | 8,853.0 (35.6%) | 8,366.0 (37.8%) | 487.0 (18.0%) | | 926.0 (17.8%) | 447.0 (17.1%) | 479.0 (18.4%) | |
| Pulmonary | 477.0 (1.9%) | 384.0 (1.7%) | 93.0 (3.4%) | | 170.0 (3.3%) | 81.0 (3.1%) | 89.0 (3.4%) | |

**Table 1** (continued)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Stool | 142.0 (0.6%) | 128.0 (0.6%) | 14.0 (0.5%) | | 26.0 (0.5%) | 12.0 (0.5%) | 14.0 (0.5%) | |
| Urine | 4,737.0 (19.1%) | 4,003.0 (18.1%) | 734.0 (27.1%) | | 1,399.0 (26.8%) | 701.0 (26.9%) | 698.0 (26.8%) | |
| **co-morbidities** | | | | | | | | |
| Myocardial infarct, n (%) | 4,310.0 (17.3%) | 3,668.0 (16.6%) | 642.0 (23.7%) | 0.18 | 1,207.0 (23.1%) | 607.0 (23.3%) | 600.0 (23.0%) | 0.01 |
| Congestive heart failure, n (%) | 7,181.0 (28.9%) | 6,131.0 (27.7%) | 1,050.0 (38.8%) | 0.24 | 1,972.0 (37.8%) | 986.0 (37.8%) | 986.0 (37.8%) | < 0.01 |
| Peripheral vascular disease, n (%) | 2,976.0 (12.0%) | 2,624.0 (11.8%) | 352.0 (13.0%) | 0.03 | 659.0 (12.6%) | 324.0 (12.4%) | 335.0 (12.9%) | 0.01 |
| Cerebrovascular disease, n (%) | 3,800.0 (15.3%) | 3,324.0 (15.0%) | 476.0 (17.6%) | 0.07 | 904.0 (17.3%) | 454.0 (17.4%) | 450.0 (17.3%) | < 0.01 |
| Chronic pulmonary disease, n (%) | 6,289.0 (25.3%) | 5,625.0 (25.4%) | 664.0 (24.5%) | 0.02 | 1,265.0 (24.3%) | 634.0 (24.3%) | 631.0 (24.2%) | < 0.01 |
| Diabetes with complications, n (%) | 2,547.0 (10.2%) | 2,044.0 (9.2%) | 503.0 (18.6%) | 0.27 | 942.0 (18.1%) | 476.0 (18.3%) | 466.0 (17.9%) | 0.01 |
| Renal disease, n (%) | 5,367.0 (21.6%) | 4,622.0 (20.9%) | 745.0 (27.5%) | 0.16 | 1,416.0 (27.2%) | 710.0 (27.2%) | 706.0 (27.1%) | < 0.01 |
| Malignant cancer, n (%) | 3,328.0 (13.4%) | 2,948.0 (13.3%) | 380.0 (14.0%) | 0.02 | 717.0 (13.8%) | 354.0 (13.6%) | 363.0 (13.9%) | 0.01 |
| Severe liver disease, n (%) | 1,866.0 (7.5%) | 1,725.0 (7.8%) | 141.0 (5.2%) | 0.10 | 291.0 (5.6%) | 150.0 (5.8%) | 141.0 (5.4%) | 0.02 |
| Delirium, n (%) | 2,289.0 (9.2%) | 1,732.0 (7.8%) | 557.0 (20.6%) | 0.37 | 964.0 (18.5%) | 469.0 (18.0%) | 495.0 (19.0%) | 0.03 |
| Sleep disorder, n (%) | 1,995.0 (8.0%) | 1,593.0 (7.2%) | 402.0 (14.8%) | 0.25 | 713.0 (13.7%) | 343.0 (13.2%) | 370.0 (14.2%) | 0.03 |
| **Severity scores and clinical interventions** | | | | | | | | |
| Sofa score, Median (Q1, Q3) | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) | 3.0 (2.0, 5.0) | 0.06 | 3.0 (2.0, 5.0) | 3.0 (2.0, 5.0) | 3.0 (2.0, 5.0) | 0.01 |
| Respiration ≥ 1, n (%) | 8,121.0 (32.7%) | 7,417.0 (33.5%) | 704.0 (26.0%) | 0.16 | 1,346.0 (25.8%) | 659.0 (25.3%) | 687.0 (26.4%) | 0.02 |
| Coagulation ≥ 1, n (%) | 8,310.0 (33.4%) | 7,410.0 (33.5%) | 900.0 (33.2%) | 0.00 | 1,766.0 (33.9%) | 891.0 (34.2%) | 875.0 (33.6%) | 0.01 |
| Liver ≥ 1, n (%) | 3,605.0 (14.5%) | 3,179.0 (14.4%) | 426.0 (15.7%) | 0.04 | 825.0 (15.8%) | 415.0 (15.9%) | 410.0 (15.7%) | 0.01 |
| Cardiovascular ≥ 1, n (%) | 15,905.0 (64.0%) | 14,246.0 (64.3%) | 1,659.0 (61.3%) | 0.06 | 3,173.0 (60.9%) | 1,577.0 (60.5%) | 1,596.0 (61.2%) | 0.01 |
| CNS ≥ 1, n (%) | 6,590.0 (26.5%) | 5,807.0 (26.2%) | 783.0 (28.9%) | 0.06 | 1,497.0 (28.7%) | 754.0 (28.9%) | 743.0 (28.5%) | 0.01 |
| Renal ≥ 1, n (%) | 8,910.0 (35.8%) | 7,677.0 (34.7%) | 1,233.0 (45.5%) | 0.22 | 2,355.0 (45.2%) | 1,184.0 (45.4%) | 1,171.0 (44.9%) | 0.01 |
| SAPS II score, Median (Q1, Q3) | 39.0 (31.0, 48.0) | 38.0 (31.0, 48.0) | 40.0 (31.0, 49.0) | 0.06 | 39.0 (31.0, 49.0) | 39.0 (31.0, 49.0) | 40.0 (31.0, 49.0) | < 0.01 |
| Charlson comorbidity index, Median (Q1, Q3) | 5.0 (3.0, 7.0) | 5.0 (3.0, 7.0) | 5.0 (3.0, 8.0) | 0.17 | 5.0 (3.0, 8.0) | 5.0 (3.0, 8.0) | 5.0 (3.0, 8.0) | 0.01 |
| Aminoglycosides, n (%) | 938.0 (3.8%) | 862.0 (3.9%) | 76.0 (2.8%) | 0.06 | 149.0 (2.9%) | 74.0 (2.8%) | 75.0 (2.9%) | < 0.01 |
| Beta lactams, n (%) | 17,850.0 (71.8%) | 15,812.0 (71.4%) | 2,038.0 (75.3%) | 0.09 | 3,913.0 (75.0%) | 1,956.0 (75.0%) | 1,957.0 (75.1%) | < 0.01 |
| Macrolides, n (%) | 3,017.0 (12.1%) | 2,556.0 (11.5%) | 461.0 (17.0%) | 0.16 | 871.0 (16.7%) | 437.0 (16.8%) | 434.0 (16.6%) | < 0.01 |
| Glycopeptides, n (%) | 16,109.0 (64.8%) | 14,203.0 (64.1%) | 1,906.0 (70.4%) | 0.13 | 3,668.0 (70.3%) | 1,832.0 (70.3%) | 1,836.0 (70.4%) | < 0.01 |
| Sulfonamides, n (%) | 200.0 (0.8%) | 174.0 (0.8%) | 26.0 (1.0%) | 0.02 | 51.0 (1.0%) | 27.0 (1.0%) | 24.0 (0.9%) | 0.01 |
| Tetracyclines, n (%) | 648.0 (2.6%) | 506.0 (2.3%) | 142.0 (5.2%) | 0.16 | 263.0 (5.0%) | 134.0 (5.1%) | 129.0 (4.9%) | 0.01 |
| Quinolones, n (%) | 4,939.0 (19.9%) | 4,717.0 (21.3%) | 222.0 (8.2%) | 0.38 | 438.0 (8.4%) | 216.0 (8.3%) | 222.0 (8.5%) | 0.01 |
| other Antibiotics use, n (%) | 708.0 (2.8%) | 613.0 (2.8%) | 95.0 (3.5%) | 0.04 | 183.0 (3.5%) | 91.0 (3.5%) | 92.0 (3.5%) | < 0.01 |
| propofol, n (%) | 14,785.0 (59.5%) | 13,014.0 (58.7%) | 1,771.0 (65.4%) | 0.14 | 3,368.0 (64.6%) | 1,675.0 (64.3%) | 1,693.0 (64.9%) | 0.01 |
| Dexmedetomidine, n (%) | 5,733.0 (23.1%) | 4,431.0 (20.0%) | 1,302.0 (48.1%) | 0.62 | 2,397.0 (46.0%) | 1,187.0 (45.5%) | 1,210.0 (46.4%) | 0.02 |
| Benzodiazepines, n (%) | 7,806.0 (31.4%) | 6,996.0 (31.6%) | 810.0 (29.9%) | 0.04 | 1,550.0 (29.7%) | 773.0 (29.7%) | 777.0 (29.8%) | < 0.01 |
| Neuromuscular blocking agents, n (%) | 1,148.0 (4.6%) | 1,023.0 (4.6%) | 125.0 (4.6%) | 0.00 | 248.0 (4.8%) | 124.0 (4.8%) | 124.0 (4.8%) | < 0.01 |

**Table 1** (continued)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Vasoactive agent, n (%) | 12,424.0 (50.0%) | 11,324.0 (51.1%) | 1,100.0 (40.6%) | 0.21 | 2,148.0 (41.2%) | 1,075.0 (41.2%) | 1,073.0 (41.2%) | < 0.01 |
| CRRT, n (%) | 1,719.0 (6.9%) | 1,449.0 (6.5%) | 270.0 (10.0%) | 0.12 | 510.0 (9.8%) | 256.0 (9.8%) | 254.0 (9.7%) | < 0.01 |
| IMV, n (%) | 13,221.0 (53.2%) | 11,961.0 (54.0%) | 1,260.0 (46.5%) | 0.15 | 2,419.0 (46.4%) | 1,193.0 (45.8%) | 1,226.0 (47.0%) | 0.03 |
| Duration of ramelteon exposure(days), Median (Q1, Q3) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 8.0 (4.0, 14.0) | 1.2 | 0.0 (0.0, 7.0) | 0.0 (0.0, 0.0) | 7.0 (4.0, 14.0) | 1.2 |
| **Outcomes** | **Overall** *N* = 24,860 | **Ramelteon unexposed** N = 22,152 | **Ramelteon exposed** *N* = 2,708 | ***P*** value | **Overall** *N* = 5,214 | **Ramelteon unexposed** *N* = 2,607 | **Ramelteon exposed** *N* = 2,607 | ***P*** value |
| In-hospital mortality, n (%) | 3,885 (15.6%) | 3,562 (16.1%) | 323 (11.9%) | < 0.001 | 816 (15.7%) | 513 (19.7%) | 303 (11.6%) | < 0.001 |
| 30-day mortality, n (%) | 4,612 (18.6%) | 4,246 (19.2%) | 366 (13.5%) | < 0.001 | 954 (18.3%) | 605 (23.2%) | 349 (13.4%) | < 0.001 |
| 90-day mortality, n (%) | 6,187 (24.9%) | 5,576 (25.2%) | 611 (22.6%) | 0.003 | 1,358 (26.0%) | 781 (30.0%) | 577 (22.1%) | < 0.001 |
| Length of hospital stay (days), Median (Q1, Q3) | 9.3 (5.7, 16.7) | 8.8 (5.4, 15.3) | 16.9 (9.7, 28.9) | < 0.001 | 13.4 (7.7, 23.8) | 10.5 (6.3, 18.6) | 16.8 (9.6, 28.8) | < 0.001 |
| Length of ICU stay (days), Median (Q1, Q3) | 3.4 (1.9, 7.0) | 3.2 (1.9, 6.6) | 5.2 (2.6, 11.0) | < 0.001 | 4.6 (2.3, 9.7) | 4.1 (2.2, 8.6) | 5.1 (2.6, 11.0) | < 0.001 |

A variable could be considered imbalanced between the groups when its SMD was >0.1

*Abbreviations:* *SMD* Standardized mean difference, *MAP* Mean blood pressure, *SpO2* Saturation of pulse oximetry, *CNS* Central nervous system, *SAPSII* Simplified acute physiology, *SOFA* Sequential Organ Failure Assessment, *WBC* White blood cell, *BUN* Blood urea nitrogen, *CRRT* Continuous renal replacement therapy, *IMV* Invasive mechanical ventilation

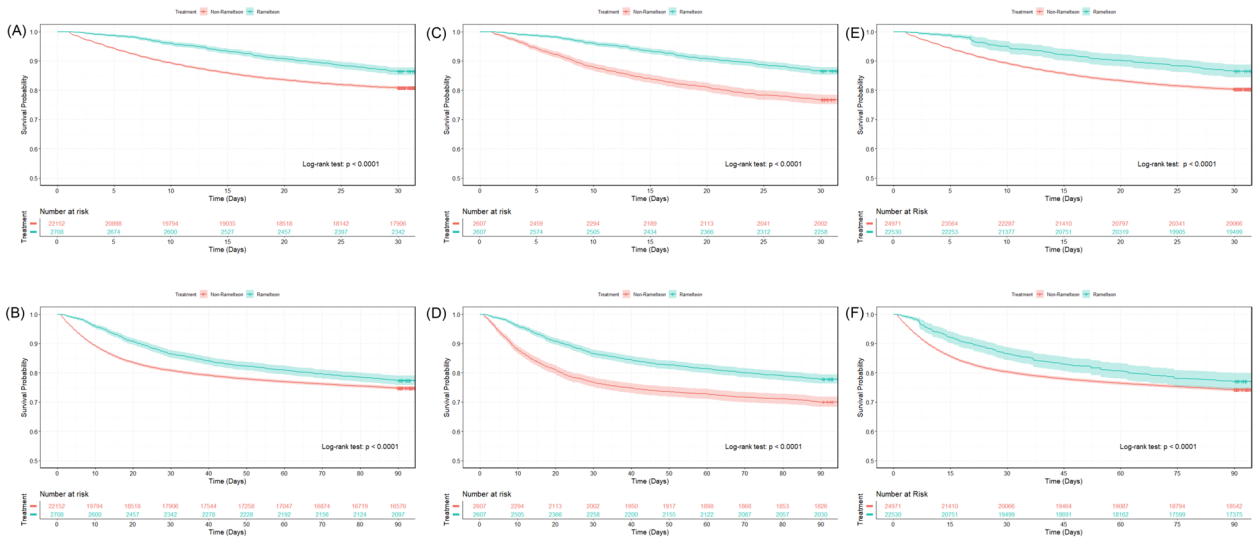


**Fig. 2** Kaplan–Meier survival curves for the two groups. A *p*-value of < 0.0001 based on the log-rank test indicates a significant difference in 30-day and 90-day mortality between the ramelteon-exposed and unexposed groups (**A**, **B**), both before and after propensity score matching (**C**, **D**) and inverse probability of treatment weighting (**E**, **F**)

exposure appeared to be linked to lower in-hospital and 90-day mortality, along with prolonged lengths of stay in the ICU and hospital. While acknowledging the limitations of retrospective data, this cohort study represents the first large-sample clinical investigation exploring the relationship between ramelteon exposure and survival in adult patients with sepsis.

Melatonin, a vital endogenous hormone, plays a crucial role in regulating circadian rhythms by activating two high-affinity G-protein-coupled receptors known as MT1 and MT2 melatonin receptors. In various experimental animal models of sepsis, melatonin has demonstrated significant anti-inflammatory, antioxidant, and antibacterial potential [12, 22, 23]. Although the exact pathologic

**Table 2** Cox regression analysis based on different models. Model 1 was corrected for demographic parameters. Model 2 builds upon Model 1 by incorporating the average values of vital signs recorded during the initial 24 h. Model 3 enhances Model 2 by including the source of infection and the maximum values of laboratory data. Model 4 extends Model 3 by adding combined disease comorbidities, while Model 5 further develops Model 4 by incorporating severity scores and clinical interventions. A *p* value < 0.001 means that a significant difference the 30-day mortality between the two groups

| Category | patients(n) | HR (95%CI) | *P*-Value |
|---|---|---|---|
| Unadjusted | 24,860 | 0.664(0.597–0.739) | < 0.001 |
| PSM | 47,321 | 0.530(0.465–0.605) | < 0.001 |
| IPTW | 5214 | 0.590(0.499–0.699) | < 0.001 |
| model 1 | 5214 | 0.529(0.463–0.603) | < 0.001 |
| model 2 | 5214 | 0.525(0.460–0.60) | < 0.001 |
| model 3 | 5214 | 0.531(0.465–0.607) | < 0.001 |
| model 4 | 5214 | 0.525(0.459–0.60) | < 0.001 |
| model 5 | 5214 | 0.528(0.461–0.603) | < 0.001 |

*Abbreviations: PSM* Propensity score matching, *IPTW* Inverse probability of treatment weighting, *HR* Hazard ratios, *CI* Confidence interval

processes of sepsis remain incompletely understood, infection, inflammation, and oxidative stress have been established as fundamental components of the disease. Melatonin holds promise in the treatment of sepsis by actively participating in these essential processes. Firstly, melatonin exhibits potential anti-infective properties and could function as a clinical agent against pathogens, including viruses [12]. Secondly, given that sepsis can induce inflammatory injuries in nearly all organ systems [24], numerous animal studies have documented the anti-inflammatory activity of melatonin in various chronic diseases [25]. Last but not least, melatonin contributes to antioxidant stress through mechanisms such as electron transfer, hydrogen transfer, the formation of radical adducts, and metal chelation [26].

While the reasons for the more significant advantage in reducing the risk of 30-day mortality in our study compared to the Sutton et al. study [17] remain speculative, various pharmacological factors may contribute to our results. Ramelteon, a synthetic melatonin ligand and high-affinity MT1 and MT2 melatonin receptor agonist is clinically recommended at a dose of 8 mg for treating sleep disorders in hospitalized and critically ill patients. Notably, the half-life of orally administered ramelteon is longer than that of melatonin [9, 11].

Although there is no published clinical evidence supporting the survival improvement in septic patients with ramelteon, preclinical studies provide a potential rationale. Notably, in animal models, ramelteon has been shown to activate nuclear factor-erythroid 2–related factor 2 (Nrf2), a key component in sepsis progression [27]. Two preclinical studies have demonstrated that ramelteon can reduce LPS-induced pathological processes by activating Nrf2 [14, 16]. Furthermore, ramelteon showed potential antiviral properties in mice infected with SARS-CoV-2 [28]. In addition, a single-center unblinded randomized controlled trial of 226 patients demonstrated that melatonin significantly improve the mortality of patients with severe COVID-19, with a mortality rate of 67% in the melatonin group and 94% in the control group [29], though notably this benefit has not been consistently reproduced in other randomized trials [30]. Furthermore, the combined use of ramelteon with vancomycin, a crucial antimicrobial agent for treating patients with staphylococcus infections, has been closely associated with a reduction in vancomycin-associated kidney injury [31].

Considering the aging trend, it is anticipated that elderly patients and those in the intermediate and late stages of sepsis will become more prevalent [32]. This implies an increased likelihood that septic patients with elevated SOFA scores will necessitate ICU support. Subgroup analyses demonstrated a consistent association between ramelteon exposure and reduced 30-day mortality in older patients(≥ 65 years), as well as in those with higher SOFA scores(≥ 5), suggesting that ramelteon exposure remains beneficial for enhancing survival in septic patients experiencing multiple organ damage. To further corroborate this observation, sensitivity analyses were conducted within the sepsis population exhibiting diverse organ injuries, demonstrating a consistent reduction in the risk of death in patients with organ dysfunction related to sepsis.

Earlier preclinical studies investigating the protective effects of ramelteon on vital organs offer theoretical support for these findings. Firstly, ramelteon inhibited LPS-induced neuro-inflammation by activating the M1 melatonin receptor in the central nervous system [33]. Secondly, ramelteon prevented LPS-induced damage to human pulmonary microvascular endothelial cells by activating the hemeoxygenase-1 or Nrf2 processes [14] and protected against ventilator-induced acute lung damage by increasing the production of IL-10 [34]. Thirdly, in rats subjected to hemorrhagic shock, ramelteon enhanced liver function, hepatic perfusion, and hepatocyte integrity [35]. Lastly, ramelteon significantly reduced myocardial infarction resulting from ischemia–reperfusion [36].

Nevertheless, when interpreting the findings of the current study, several potential limitations should be acknowledged. Firstly, As a retrospective observational study, the findings are susceptible to residual bias and unmeasured confounding variables, despite the application of PSM, IPTW and Cox multivariable

| Variable | Count,n | Percent,% | HR (95% CI) | P value | P for interaction |
|---|---|---|---|---|---|
| Overall | 5214 | 100 | 0.53 (0.46 to 0.61) | <0.001 | |
| Age | | | | | 0.004 |
| ≥ 65 | 3186 | 61.1 | 0.58 (0.50 to 0.67) | <0.001 | |
| < 65 | 2028 | 38.9 | 0.35 (0.26 to 0.48) | <0.001 | |
| SOFA score | | | | | 0.927 |
| >= 5 | 858 | 16.5 | 0.53 (0.40 to 0.71) | <0.001 | |
| < 5 | 4356 | 83.5 | 0.53 (0.46 to 0.61) | <0.001 | |
| Charlson comorbidity index | | | | | 0.051 |
| > 4 | 3207 | 61.5 | 0.56 (0.49 to 0.65) | <0.001 | |
| • 4 | 2007 | 38.5 | 0.39 (0.29 to 0.55) | <0.001 | |
| Delirium | | | | | 0.276 |
| No | 4250 | 81.5 | 0.52 (0.45 to 0.59) | <0.001 | |
| Yes | 964 | 18.5 | 0.62 (0.45 to 0.86) | 0.004 | |
| Vasoactive agent | | | | | 0.415 |
| No | 3066 | 58.8 | 0.56 (0.47 to 0.66) | <0.001 | |
| Yes | 2148 | 41.2 | 0.50 (0.41 to 0.61) | <0.001 | |
| Neuromuscular blocking agents | | | | | 0.012 |
| No | 4966 | 95.2 | 0.55 (0.48 to 0.63) | <0.001 | |
| Yes | 248 | 4.8 | 0.24 (0.13 to 0.46) | <0.001 | |
| Propofol | | | | | <0.001 |
| No | 1846 | 35.4 | 0.87 (0.71 to 1.06) | 0.163 | |
| Yes | 3368 | 64.6 | 0.38 (0.32 to 0.45) | <0.001 | |
| Dexmedetomidine | | | | | <0.001 |
| No | 2817 | 54 | 0.75 (0.64 to 0.89) | 0.001 | |
| Yes | 2397 | 46 | 0.31 (0.25 to 0.39) | <0.001 | |
| Benzodiazepines | | | | | <0.001 |
| No | 3664 | 70.3 | 0.65 (0.55 to 0.76) | <0.001 | |
| Yes | 1550 | 29.7 | 0.34 (0.27 to 0.43) | <0.001 | |
| Invasive mechanical ventilation | | | | | <0.001 |
| No | 2795 | 53.6 | 0.76 (0.65 to 0.90) | 0.001 | |
| Yes | 2419 | 46.4 | 0.29 (0.23 to 0.37) | <0.001 | |
| Continuous renal replacement therapy | | | | | 0.421 |
| No | 4704 | 90.2 | 0.54 (0.47 to 0.63) | <0.001 | |
| Yes | 510 | 9.8 | 0.46 (0.34 to 0.62) | <0.001 | |

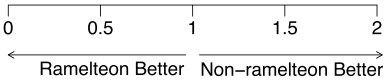


**Fig. 3** Subgroup analysis based on PSM cohort. A *p* value < 0.001 means that a significant difference the 30-day mortality between the two groups, and a *p*-value for interaction less than 0.05 indicates a potential interaction

analysis.Secondly, it is important to note that despite excluding patients with a history of melatonin exposure from the database, there remains a possibility of non-prescribed drug exposure to synthetic melatonin, potentially as a dietary supplement.Thirdly, Clinical outcomes in patients with sepsis are closely linked to the quality of care provided. It is important to recognize that MIMIC-IV, as a single-center database, may not fully represent the broader population from which these cases are drawn. Fourth, At the end of the study, we repeated the PSM, incorporating hospital and ICU stay lengths as covariates once again. This re-evaluation confirmed the stability of our conclusions. However, it remains possible that patients in the ramelteon exposure group were inherently less aggressive or received more attention compared to those who had longer hospital stays. Lastly,We did not determine the optimal duration of ramelteon exposure, although we made attempts to investigate the relationship between ramelteon exposure duration and 30-day mortality risk. To establish a more robust understanding, additional high-quality randomized studies with larger sample sizes are imperative to comprehensively investigate the impact of ramelteon exposure on survival outcomes in septic patients within the ICU.

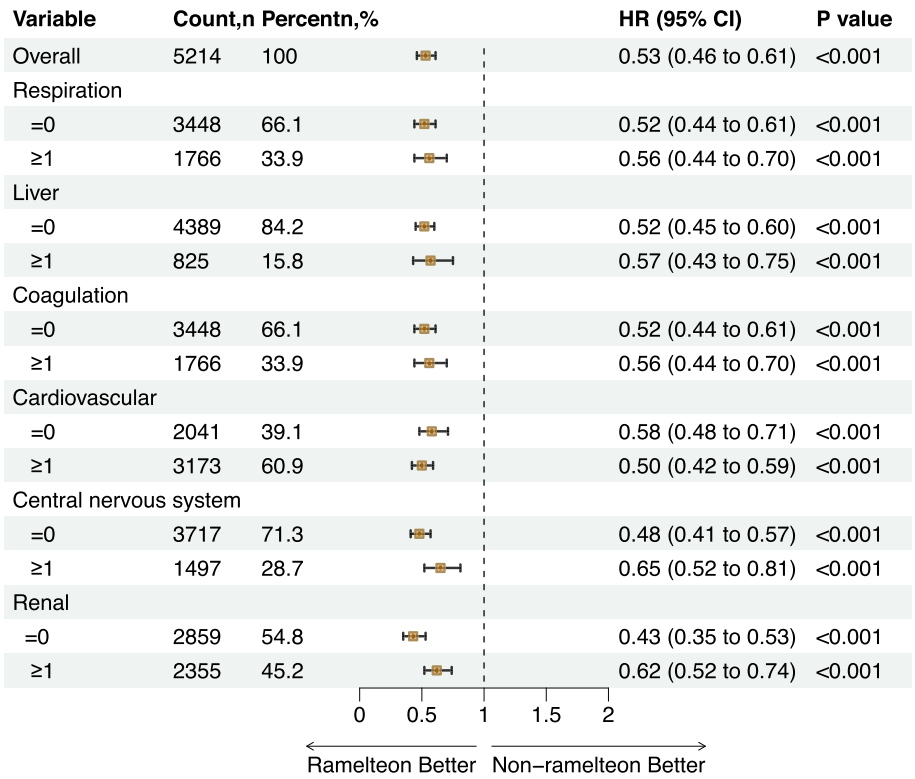


**Fig. 4** Sensitivity analysis for the severity scores based on PSM cohort. A $p$ value < 0.001 means that a significant difference the 30-day mortality in different subgroups between ramelteon exposed and unexposed group

## Conclusions

Overall, this retrospective study, based on a large sample size, revealed an association between ramelteon exposure and 30-day and 90-day mortality in patients with sepsis. Additionally, there is limited evidence indicating that ramelteon exposure may be linked to decreased in-hospital mortality but increased length of ICU time and overall length of stay when compared with the ramelteon-unexposed group. However, it is crucial to acknowledge the inherent limitations of statistical methodologies and data sources in observational studies. To establish a more robust and definitive understanding, further investigation through rigorous randomized controlled trials is warranted.

### Abbreviations

| | |
|---|---|
| ICU | Intensive care unit |
| MIMIC-IV | Medical Information Mart for Intensive Care IV |
| PSM | Propensity score matching |
| IPTW | Inverse probability of treatment weighting |
| K–M | Kaplan–Meier |
| MTs | Melatonin receptors |
| LPS | Lipopolysaccharide |
| SOFA | Sequential Organ Failure Assessment |
| SAPSII | Simplified acute physiology score |
| IMV | Invasive mechanical ventilation |
| CRRT | Continuous renal replacement therapy |
| SD | Standard deviation |
| IQR | Interquartile range |
| HR | Hazard ratios |
| CIs | Confidence intervals |
| SMD | Standardized mean difference |
| MAP | Mean blood pressure |
| $SpO_2$ | Saturation of pulse oximetry |
| COPD | Chronic obstructive pulmonary disease |
| WBC | White blood cell |
| BUN | Blood urea nitrogen |
| CNS | Central nervous system |
| Nrf2 | The nuclear factor-erythroid 2–related factor 2 |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02851-9.

Supplementary Material 1.

### Acknowledgements

Not applicable.

### Data source and ethics statement

The Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) institutional review boards authorized this investigation, and informed consent was waived.

### Authors' contributions

Yun-Yang Han: Conceptualization, Formal analysis,Investigation,Methodology, Software, Writing – original draft. Yu Tian: Data curation, Formal analysis, Software, Writing – original draft. Bing-Cheng Zhao: Formal analysis, Methodology, Supervision, Writing – review & editing. Ke-Xuan Liu: Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Authorization for this investigation was granted by the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) institutional review boards, with informed consent waived. Database access was granted to a researcher (HYY) who completed the Collaborative Institutional Training Initiative test (name ID: 10112186, record ID: 42408105).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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