Original Article

Association between ondansetron use and mortality of patients on mechanical ventilation in the intensive care unit: a retrospective cohort study

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Background: Basic studies show that selective 5-hydroxytryptamine type 3 (5-HT$_3$) serotonin-receptor antagonists can protect organs from inflammatory injury and have shown lung protection. Whether 5-HT$_3$ receptor antagonists ondansetron benefits patients with mechanical ventilation is unclear in the intensive care unit (ICU).

Methods: The Medical Information Mart for Intensive Care-IV (MIMIC-IV) database was reviewed to identify patients on mechanical ventilation (aged >16 years) in the ICU, which was divided into two groups according to whether ondansetron is used. Demographic characteristics, medical history data, clinical parameters, diagnosis and treatment measures were included as covariates. Ondansetron use was defined as any kind of ondansetron administration regardless of the dose before the induction of mechanical ventilation. The primary outcome was in-hospital death. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by multivariable Cox regression. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were performed to further adjust for confounding factors. Kaplan-Meier (KM) curves with log-rank test were also performed.

Results: A total of 18,566 patients on mechanical ventilation were included (5,735 with ondansetron use). The overall in-hospital mortality rate of patients on mechanical ventilation was 18.9% (3,512/18,566). Approximately 13.0% (746/5,735) and 21.6% (2,766/12,831) in-hospital mortality rates occurred in the ondansetron and non-ondansetron use groups, respectively. Multivariable regression indicated that ondansetron usage was associated with a 33% and 32% lower risk of in-hospital and 60-day death (HR =0.77, 95% CI: 0.70–0.85, P<0.001; HR =0.68, 95% CI: 0.62–0.75, P<0.001) in the whole sample. Multivariable regression post-PSM indicated that ondansetron usage was associated with a 38% and 31% lower risk of in-hospital and 60-day death (HR =0.62, 95% CI: 0.56–0.68, P<0.001; HR =0.69, 95% CI: 0.62–0.77, P<0.001). Log-rank test for the KM curve of ondansetron and 60-day death was statistically significant (P<0.001). The duration of ventilator use pre- and post-PSM was statistically different (P<0.001 and P=0.007) in the two groups.

Conclusions: Ondansetron usage was significantly associated with a lower mortality risk of ventilated patients in the ICU. The 5-HT3 receptor antagonist use is may be new potential adjunctive therapeutic strategy for patients on mechanical ventilation in the ICU.

Introduction

The mortality rate of patients on mechanical ventilation in the intensive care unit (ICU) is high (1,2). Some risk factors had been demonstrated to associate with mortality in patients on mechanical ventilation in the ICU, such as gender, age, laboratory findings and comorbidities including hypertension, diabetes, heart disease, chronic obstructive pulmonary disease, chronic kidney disease and malignant neoplasm (3,4).

The 5-hydroxytryptamine (5-HT) receptors have been demonstrated as involved in cigarette smoke-induced airway inflammation, mucus hypersecretion, and airway remodeling in a murine model of chronic obstructive pulmonary disease (5,6), and also involved in the occurrence of sepsis (7) and acute respiratory distress syndrome (8), which are critical illnesses often requiring ventilator-assisted respiration in the ICU. Furthermore, inhibition of lung-derived serotonin attenuates pulmonary hypertension in mice (9). Basic studies have shown that 5-HT receptor antagonists can protect the lungs. For example, they attenuated ischemia-reperfusion injury after lung preservation in a rabbit model (10), and also reduced myofibroblast differentiation and connective tissue deposits in fibrosing interstitial lung diseases (11).

Ondansetron, a 5-HT type 3 ($5\text{-}HT_3$) receptor antagonist, is a widely used antiemetic and a highly safe medication even for pregnant women (12-15). Neuroepithelial bodies in the mammalian lung express functional $5\text{-}HT_3$ receptors (16), and recently $5\text{-}HT_3$ receptor antagonists were demonstrated to have a broad therapeutic window (17). Importantly, they protected the lungs from polymicrobial sepsis-induced acute lung injury in mice (18), and regulate cell proliferation, migration, and invasion in lung cancer (19-21) and even reducing the death risk (7). Whether $5\text{-}HT_3$ receptor antagonists ondansetron benefits patients with mechanical ventilation in clinical is unclear. Therefore, we conducted a retrospective cohort study to assess the effects of ondansetron on reducing the mortality rate of patients on ventilation in the ICU, which would help to find new potential adjunctive therapeutic strategy for patients on mechanical ventilation. We present the following article in accordance with the STROBE reporting checklist (22) (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6256/rc).

Methods

From the Medical Information Mart for Intensive Care-IV (MIMIC-IV) (version 0.4) database (23,24), we enrolled a cohort of patients on mechanical ventilation administered ondansetron or not. The MIMIC-IV is a real-world and publicly available clinical database at the Beth Israel Deaconess Medical Center. We obtained approval to use the database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study design and study population

This is a retrospective cohort study. All patients aged >16 years on mechanical ventilation in the ICU were included. Patients receiving ondansetron only after induction of mechanical ventilation or during out-of-ICU stay were excluded. Only the data of their first ICU

Highlight box

Key findings
- Ondansetron usage was significantly associated with a lower mortality risk of ventilated patients in the ICU.

What is known and what is new?
- Ondansetron, a 5-HT3 receptor antagonist, is a widely used antiemetic drug and a highly safe medication even for pregnant women.
- This retrospective cohort study was conducted to assess the effects of ondansetron on mortality of patients on ventilation in the ICU.

What is the implication, and what should change now?
- The MIMIC-IV database was reviewed to identify patients on mechanical ventilation in the ICU. Our results suggest that the use of 5-HT3 receptor antagonists may be a new potential adjuvant treatment strategy for patients on mechanical ventilation in the ICU.

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stay were included for patients admitted to the ICU more than once.

Definitions and outcomes

Ventilator-associated pneumonia (VAP) was defined as pneumonia developing in patients on mechanical ventilation for at least 48 h and 48 h after extubation. VAP data were extracted from the "Diagnosis" section in the MIMIC-IV database. Ondansetron use was defined as any kind of ondansetron administration regardless of the dose before the induction of mechanical ventilation during the ICU stay. The primary outcome was in-hospital death. Secondary outcomes were the VAP incidence, 60-day mortality rate, ventilator duration, and vasopressor duration.

Covariates

Demographic characteristics, as well as clinical, and medical history data for the first 24 h after the ICU admission were extracted. The simplified acute physiology score (SAPS) II (25), sequential organ failure assessment (SOFA) score (26), and Glasgow coma scale (GCS) score (27) were calculated. The ICU diagnosis, treatment measures, and antibiotic drugs administered throughout the entire ICU stay were also extracted (*Table 1*). Vasopressors used included dobutamine, vasopressin, phenylephrine, epinephrine, dopamine, and norepinephrine. Disease diagnosis was extracted from the "Diagnosis" section in the MIMIC-IV database. As for the antibiotics, carbapenems (meropenem), glycopeptide (vancomycin), β-lactams (ceftriaxone, cefotaxime, and cefepime), and aminoglycosides (gentamicin and amikacin) were extracted for our analysis. These covariates included as much basic information and clinical characteristics of patients as possible and were designed according to other related studies (3,4).

Statistical analysis

Continuous variables are presented as the median and interquartile range (IQR), and categorical variables as numbers and percentages (%). Cox proportional hazard analysis was used to examine the association between in-hospital mortality, 60-day mortality and ondansetron use with hazard ratios (HRs) and their 95% confidence intervals (CIs). The confounders, including baseline clinical parameters and demographic characteristics in *Table 1*, were adjusted. To further consider the robustness of our results,

1:1 nearest propensity score matching (PSM) and an inverse probability of treatment weighting (IPTW) were performed with the same confounders adjusted in the multivariate logistic and Cox models. Using PSM (with a caliper of 0.2), individuals were matched, and the balance between matching groups was tested with the standard mean difference. Using the IPTW method, a pseudo-population was generated based on the propensity score and the HRs were calculated based on it. Kaplan-Meier (KM) curves with log-rank test were performed. Furthermore, subgroup analyses stratified by age, sex, surgery, acute kidney injury (AKI), sepsis, pneumonia, malignancy, and congestive heart failure (CHF) were performed to assess the robustness of the results. The percentage of missing value of all the participants is presented in Table S1. The Percentage of Missing Value of all the participants are less than 1%, except for lactic acid with 17.89% in non-ondansetron group and 15.01% in ondansetron group. Missing values were under the assumption of missing at random and imputed by multivariate imputation by chained equations. All analyses were performed using R (4.0.2) and Statistical Analysis System (9.4). A P value of <0.05 (two-sided) was considered statistically significant.

Results

Main result

In this study, 18,566 eligible patients on mechanical ventilation were identified, and of them 5,735 (30.89%) were administered ondansetron during their ICU stay. The flowchart of study patients is presented in *Figure 1*. All between-group comparisons used the non-ondansetron group as the reference unless otherwise indicated. The overall in-hospital mortality rate of patients on mechanical ventilation was 18.9% (3,512/18,566). Approximately 13.0% (746/5,735) and 21.6% (2,766/12,831) in-hospital mortality rates occurred in the ondansetron and non-ondansetron use groups, respectively (*Table 2*). HRs of the two groups in the multivariable Cox model before matching and after IPTW and PSM were 0.77 (95% CI: 0.70–0.85, P<0.001), 0.86 (95% CI: 0.78–0.95, P=0.002), and 0.62 (95% CI: 0.56–0.68, P<0.001), respectively, demonstrating a significant beneficial effect of ondansetron use on in-hospital death of patients on mechanical ventilation (*Table 3*).

Secondary result

The 60-day hospital mortality rate was 18.8%

Table 1 Baseline characteristics of the two groups before and after PSM

Characteristics	Total (n=18,566)	Before PSM			After PSM		
		Non-ondansetron (n=12,831)	Ondansetron (n=5,735)	SMD	Non-ondansetron (n=4,739)	Ondansetron (n=4,739)	SMD
Demographic data							
Age (years), mean (SD)	67.3 (56.4–77.5)	67.6 (56.1–78.6)	66.8 (56.9–75.4)	0.035	65.41 (15.74)	65.27 (14.68)	0.009
Sex (male), n (%)	11,542 (62.2)	8,069 (62.9)	3,473 (60.6)	0.048	2,864 (60.4)	2,871 (60.6)	0.003
Ethnicity (non-White), n (%)	6,731 (36.3)	4,950 (38.6)	1,781 (31.1)	0.158	3,210 (67.7)	3,209 (67.7)	0.001
Married, n (%)	8,646 (46.6)	5,627 (43.9)	3,019 (52.6)	0.177	2,390 (50.4)	2,409 (50.8)	0.008
Insurance (Medicare), n (%)	9,370 (50.5)	6,720 (52.4)	2,650 (46.2)	0.124	2,259 (47.7)	2,260 (47.7)	<0.001
Admission type (emergency), n (%)	8,996 (48.5)	7,177 (55.9)	1,819 (31.7)	0.503	1,823 (38.5)	1,753 (37.0)	0.03
Weight (kg), median (IQR)	81.7 (69.0–96.8)	81.0 (68.5–96.3)	83.0 (70.0–97.8)	0.050	69 (81.6–96.8)	69.9 (83.0–97.3)	0.006
Clinical data							
White blood cells (×10⁹), median (IQR)	12.1 (9.0–15.8)	11.8 (8.8–15.5)	12.7 (9.6–16.2)	0.079	9.2 (12.3–16.0)	9.1 (12.1–15.7)	0.006
Platelets (×10¹²), median (IQR)	177.7 (131.3–239.5)	185.0 (136.3–246.0)	162.8 (123.0–221.3)	0.150	127.7 (171.5–232.5)	126.5 (168.7–228.5)	0.01
Creatinine (mg/dL), median (IQR)	1.0 (0.8–1.4)	1.0 (0.8–1.5)	0.9 (0.7–1.3)	0.069	0.7 (1.0–1.4)	0.7 (1.0–1.4)	0.016
Lactate (mmol/L), median (IQR)	1.9 (1.4–2.7)	1.9 (1.4–2.8)	1.9 (1.5–2.6)	0.107	1.4 (1.9–2.6)	1.4 (1.9–2.5)	0.028
SAPS II score, median (IQR)	32.0 (24.0–41.0)	32.0 (25.0–42.0)	30.0 (23.0–38.0)	0.207	24.0 (31.0–40.0)	24.0 (31.0–39.0)	0.042
SOFA score, median (IQR)	5.0 (4.0–7.0)	5.0 (3.0–7.0)	5.0 (4.0–7.0)	0.213	4.0 (5.0–7.0)	4.0 (5.0–7.0)	0.012
GCS score, median (IQR)	14.0 (9.0–15.0)	14.0 (8.0–15.0)	14.0 (10.0–15.0)	0.202	9.0 (14.0–15.0)	10.0 (14.0–15.0)	0.02
AKI, n (%)	10,979 (59.1)	7,430 (57.9)	3549 (61.9)	0.081	2,887 (60.9)	2,869 (60.5)	0.008
Medical history, n (%)							
Hypertension	7,706 (41.5)	5,160 (40.2)	2,546 (44.4)	0.085	2,014 (42.5)	2,031 (42.9)	0.007
Diabetes	5,028 (27.1)	3,334 (26.0)	1,694 (29.5)	0.079	1,330 (28.1)	1,337 (28.2)	0.003
Chronic heart failure	4,610 (24.8)	3,235 (25.2)	1,375 (24.0)	0.029	1,152 (24.3)	1,137 (24.0)	0.007
CKD	3,059 (16.5)	2,052 (16.0)	1,007 (17.6)	0.042	817 (17.2)	816 (17.2)	0.001
Chronic liver disease	2,001 (10.8)	1,390 (10.8)	611 (10.7)	0.006	330 (7.0)	313 (6.6)	0.014
COPD	4,195 (22.6)	3,026 (23.6)	1,169 (20.4)	0.077	1,001 (21.1)	1,001 (21.1)	0.001
Malignancy	1,690 (9.1)	995 (7.8)	695 (12.1)	0.146	571 (12.0)	550 (11.6)	0.014
Diagnosis, n (%)							
Surgery	7,604 (41.1)	4,238 (33.2)	3,366 (59.0)	0.537	2,466 (52.0)	2,488 (52.5)	0.009
Sepsis	2,910 (15.7)	2,198 (17.1)	712 (12.4)	0.133	685 (14.5)	643 (13.6)	0.026
ACS/AMI	283 (1.5)	231 (1.8)	52 (0.9)	0.077	51 (1.1)	51 (1.1)	<0.001
Pneumonia	3,729 (20.1)	2,795 (21.8)	934 (16.3)	0.140	867 (18.3)	854 (18.0)	0.007

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=18,566)	Before PSM			After PSM		
		Non-ondansetron (n=12,831)	Ondansetron (n=5,735)	SMD	Non-ondansetron (n=4,739)	Ondansetron (n=4,739)	SMD
Treatments							
Fluid input on day 2 (L), median (IQR)	6.9 (4.3–9.8)	6.5 (3.8–9.8)	7.5 (5.6–9.9)	0.156	4.9 (7.3–10.2)	4.9 (7.3–10.1)	0.014
CRRT, n (%)	930 (5.0)	607 (4.7)	323 (5.6)	0.041	280 (5.9)	275 (5.8)	0.004
Glucocorticoids, n (%)	3,277 (17.7)	2,183 (17.0)	1,094 (19.1)	0.054	743 (15.7)	965 (20.4)	0.122
Vasopressor use, n (%)	9,767 (52.6)	6,524 (50.8)	3,243 (56.5)	0.115	2,586 (54.6)	2,584 (54.5)	0.001
Metoclopramide, n (%)	4,920 (26.5)	3,624 (28.2)	1,296 (22.6)	0.260	1,392 (29.4)	1,249 (26.4)	0.067
Antibiotics, n (%)							
Carbapenems	1,416 (7.6)	876 (6.8)	540 (9.4)	0.095	469 (9.9)	457 (9.6)	0.009
Glycopeptide	11,489 (61.9)	7,652 (59.6)	3,837 (66.9)	0.151	3,160 (66.7)	3,117 (65.8)	0.019
β-lactams	5,647 (30.4)	4,165 (32.5)	1,482 (25.8)	0.146	1,407 (29.7)	1,367 (28.8)	0.019
Aminoglycosides	222 (1.2)	126 (1.0)	96 (1.7)	0.060	68 (1.4)	74 (1.6)	0.01

PSM, propensity score matching; SMD, standard mean difference; SD, standard deviation; IQR, interquartile range; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; GCS, Glasgow coma scale; AKI, acute kidney disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ACS/AMI, acute coronary syndrome/acute myocardial infarction; CRRT, continuous renal replacement therapy.
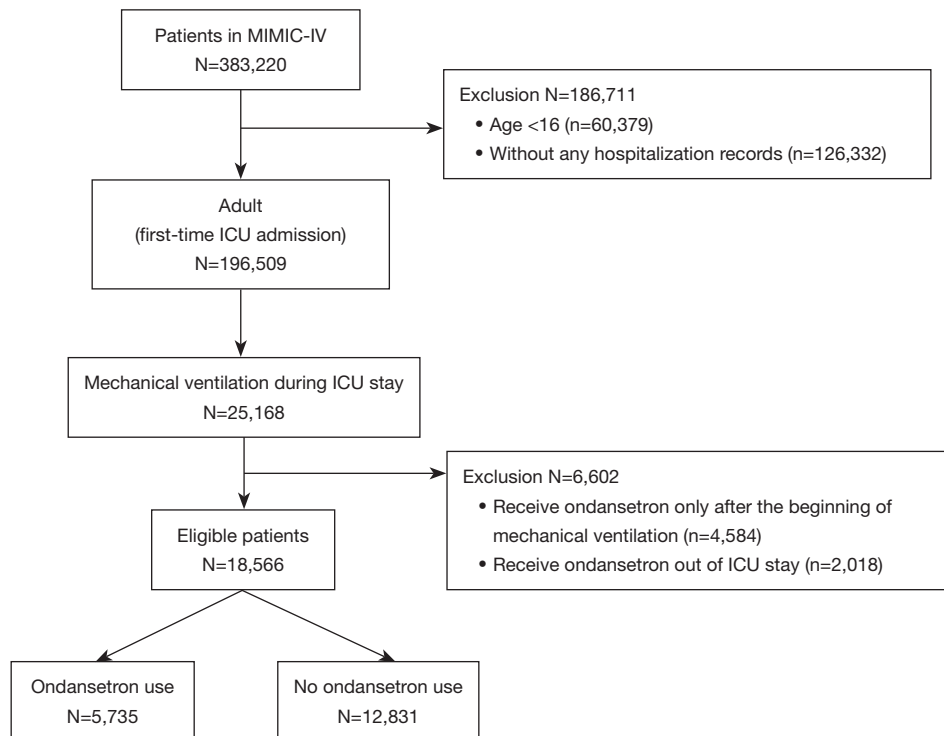

Figure 1 Flowchart of the study. MIMIC-IV, Medical Information Mart for Intensive Care-IV; ICU, intensive care unit.

Table 2 Outcomes for the two groups before and after PSM

Outcome	Total	Non-ondansetron	Ondansetron	P value
Before PSM				
Patients, n	18,566	12,831	5,735	
In-hospital mortality, n (%)	3,512 (18.9)	2,766 (21.6)	746 (13.0)	<0.001
60-day mortality, n (%)	3,486 (18.8)	2,752 (21.4)	734 (12.8)	<0.001
VAP, n (%)	860 (4.6)	647 (5.0)	213 (3.7)	<0.001
Duration of ventilator (h), median (IQR)	18.0 (6.0–65.5)	20.3 (7.0–73.9)	12.7 (4.9–43.9)	<0.001
Duration of vasopressor (h), median (IQR)	24.2 (10.0–55.2)	24.2 (9.9–53.8)	24.6 (10.1–58.4)	0.047
After PSM				
Patients, n	9,478	4,739	4,739	
In-hospital mortality, n (%)	1,657 (17.5)	959 (20.2)	698 (14.7)	<0.001
60-day mortality, n (%)	1,643 (17.3)	955 (20.2)	688 (14.5)	<0.001
VAP, n (%)	412 (4.3)	216 (4.6)	196 (4.1)	0.339
Duration of ventilator (h), median (IQR)	17.0 (5.78–64.0)	17.2 (5.7–64.1)	16.8 (5.9–64.0)	0.007
Duration of vasopressor (h), median (IQR)	14.5 (6.1–31.6)	14.8 (6.2–32.0)	14.5 (6.1–31.2)	0.170

PSM, propensity score matching; VAP, ventilator-associated pneumonia; IQR, interquartile range.

Table 3 Association between ondansetron use and outcomes

Model	HR	95% CI	P value
In-hospital mortality			
Unadjusted	0.50	0.46–0.55	<0.001
Multivariable	0.77	0.70–0.85	<0.001
IPTW	0.86	0.78–0.95	0.002
PSM	0.62	0.56–0.68	<0.001
60-day mortality			
Unadjusted	0.56	0.51–0.60	<0.001
Multivariable	0.68	0.62–0.75	<0.001
IPTW	0.76	0.68–0.83	<0.001
PSM	0.69	0.62–0.77	<0.001

Unadjusted: without adjustment; multivariable adjusted: adjusted for the baseline variables shown in *Table 1*. HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weighting; PSM, propensity score matching.

(3,486/18,566), with 12.8% (734/5,735) and 21.4% (2,752/12,831) in the ondansetron and non-ondansetron use groups, respectively. HRs of the two groups in the multivariable Cox model before matching and after IPTW and PSM were 0.68 (95% CI: 0.62–0.75, P<0.001), 0.76 (95% CI: 0.68–0.83, P<0.001), and 0.69 (95% CI: 0.62–0.77, P<0.001), respectively, demonstrating a significant beneficial effect of the ondansetron use on the 60-day mortality rate for patients on mechanical ventilation (*Table 3*). Log-rank test for the KM curve of ondansetron use and the 60-day mortality rate before and after PSM was statistically significant (P<0.0001) (*Figure 2*).
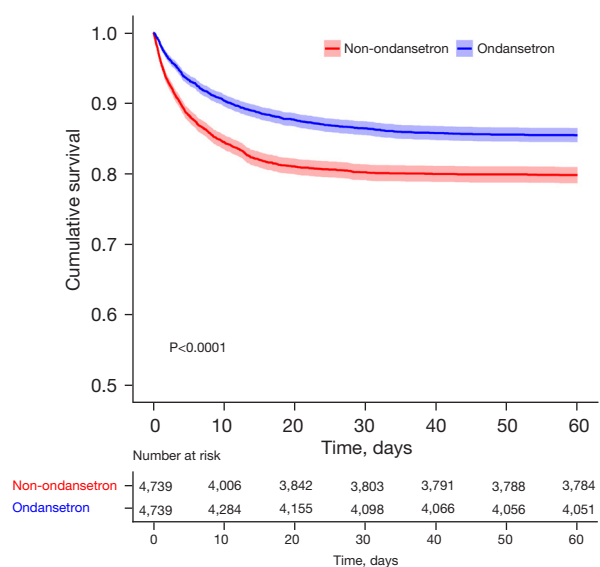
Figure 2 Log-rank test for association of ondansetron use and 60-day mortality rate of ventilated patients after PSM. PSM, propensity score matching.

The overall VAP incidence was 4.6% (860/18,566), with 3.7% (213/5,735) and 5.0% (647/12,831) in the ondansetron and non-ondansetron use groups, respectively (P<0.001) (*Table 2*). Moreover, the duration of ventilator use in the ondansetron group was statistically shorter than that in the non-ondansetron group [12.7 (4.9–43.9) *vs.* 20.3 (7.0–73.9), P<0.001] (*Table 2*). A statistical difference was also observed in the duration of ventilator use after PSM [16.8 (5.9–64.0) *vs.* 17.2 (5.7–64.1), P=0.007] in the two groups (*Table 2*). However, although VAP and vasopressor use duration decreased in the ondansetron group, there was no statistical difference of VAP (4.1% *vs.* 4.6%, P=0.339) and vasopressor use duration [14.5 (6.1–31.2) *vs.* 14.8 (6.2–32.0), P=0.170] in the two groups (*Table 2*).

Subgroup and sensitivity analyses

Ondansetron has been associated with reduced mortality rates in critically ill patients using a ventilator, but it is not known whether this association exists in ventilated patients with different status. Therefore, we performed a subgroup analysis. As shown in *Figure 3*, among all the different subgroups, such as the subgroups of ventilated patients with and without sepsis, ondansetron use was associated with lower in-hospital mortality rates. For the association between ondansetron use and death, no interaction

between stratification variables (age, sex, surgery, AKI, sepsis, pneumonia, malignancy, CHF, and SOFA) and ondansetron use was observed (*Figure 3*). Moreover, sensitivity analysis was performed to assess the association between ondansetron use within 48 h after ICU admission and outcomes, with the results showing similar conclusions (Table S2).

Discussion

This retrospective cohort study found that ondansetron use was associated with reduced mortality rates for patients on mechanical ventilation. This association was robust because of the additional models for controlling the indicated bias and subgroups stratified by age, sex, surgery, AKI, sepsis, pneumonia, malignancy, CHF, and SOFA. We believe this finding can be extended to the larger population of ICU ventilated patients.

The worldwide VAP incidence is 15.6% (28), but in our study of 18,566 patients on mechanical ventilation in the MIMIC-IV database during 2008 and 2019, VAP occurred in 4.63% (860/18,566) of patients. Consistent with our finding, Su *et al.* (29) analyzed 9,457 patients on mechanical ventilation during 2001 and 2012 in the MIMIC-III database and found that the VAP incidence was 4.42% (418/9,457). VAP incidence varies in critical patients with different diseases (30,31), and there exists certain diagnostic difficulties. Maybe because of the above reasons, the record of VAP in the "Diagnosis" section in the MIMIC-IV database is more likely unrecorded, and therefore, the VAP incidence was lower in our study than that in other previous studies. Furthermore, although no statistical difference was observed in the two groups after PSM in this study, the VAP incidence tended to decrease in the ondansetron group before and after PSM. Madineh *et al.*'s (32) study also showed that VAP in the ondansetron group was less prevalent than in the non-ondansetron group (12.5% *vs.* 15%). However, the sample size of 40 participants in their study was relatively small.

In obstetric-related studies, 4 mg of intravenous ondansetron reduced the median effective dose (ED_{50}) of a prophylactic phenylephrine infusion by approximately 26% in patients undergoing cesarean delivery under combined spinal-epidural anesthesia (33), and prophylactic ondansetron of 8 mg reduced the number of hypotensive events per patient by 50% during elective cesarean delivery under spinal anesthesia in a double-blinded, randomized, placebo-controlled trial (34). Ondansetron affected
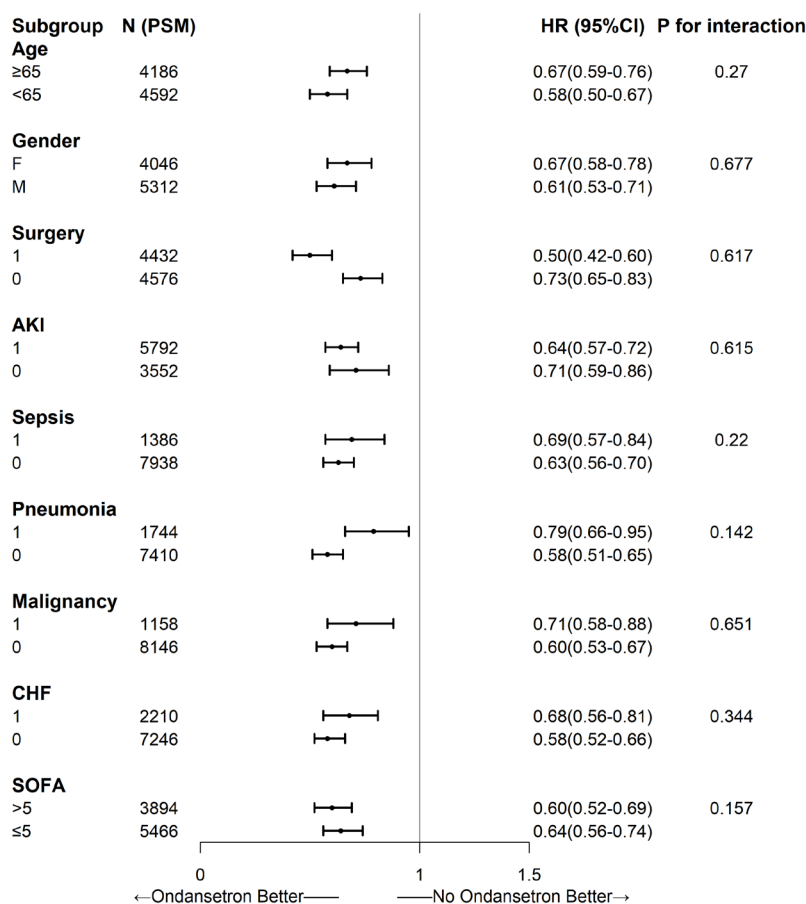
Subgroup	N (PSM)	HR (95%CI)	P for interaction
Age			
≥65	4186	0.67(0.59-0.76)	0.27
<65	4592	0.58(0.50-0.67)	
Gender			
F	4046	0.67(0.58-0.78)	0.677
M	5312	0.61(0.53-0.71)	
Surgery			
1	4432	0.50(0.42-0.60)	0.617
0	4576	0.73(0.65-0.83)	
AKI			
1	5792	0.64(0.57-0.72)	0.615
0	3552	0.71(0.59-0.86)	
Sepsis			
1	1386	0.69(0.57-0.84)	0.22
0	7938	0.63(0.56-0.70)	
Pneumonia			
1	1744	0.79(0.66-0.95)	0.142
0	7410	0.58(0.51-0.65)	
Malignancy			
1	1158	0.71(0.58-0.88)	0.651
0	8146	0.60(0.53-0.67)	
CHF			
1	2210	0.68(0.56-0.81)	0.344
0	7246	0.58(0.52-0.66)	
SOFA			
>5	3894	0.60(0.52-0.69)	0.157
≤5	5466	0.64(0.56-0.74)	

←Ondansetron Better——   ——No Ondansetron Better→

Figure 3 Subgroup analyses in different subgroups and Interaction analysis between stratification variables and ondansetron use. PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; AKI, acute kidney disease; CHF, chronic heart failure; SOFA, sequential organ failure assessment.

the plasma vasopressin level in a study of patients with cancer, indicating that serotoninergic mechanisms, which regulate vasopressin secretion in humans, may activate serotonin receptors that ondansetron recognizes (35). In our study, ondansetron use was also associated with shorter vasopressor duration before PSM, although this result was not statistically significant after PSM.

The mortality rate of patients on mechanical ventilation is high. It was 26.0% in a study of a machine learning model for predicting in-hospital death of patients on mechanical ventilation following a moderate to severe traumatic brain injury (1). In critically ill children on mechanical ventilation, the in-hospital mortality rate varies from 7% to 33.7% (36). In our study, the in-hospital mortality rate of patients on mechanical ventilation was 21.6%, which was statistically decreased to 13.0% in the ondansetron group.

There are several possible reasons for patients on mechanical ventilation benefiting from ondansetron use. First, ondansetron may reduce excessive inflammatory reactions in the lungs. Inflammation plays a critical role in the need for invasive mechanical ventilation (37), ventilator-induced lung injury (38-40), prolonged mechanical ventilation (41,42), and death risk of patients on mechanical ventilation (37,43). Recently, 5-HT$_3$ receptor antagonists were suggested as important potential agents for regulating inflammation and immune disorders (7). Administration of granisetron to septic mice was shown to significantly decrease lung damage by suppressing macrophage C-X-C motif chemokine ligand (CXCL)1/CXCL2 expression and neutrophil recruitment (18). Second, different from patients who undergo elective surgery with an empty stomach and under general anesthesia, critically ill patients who
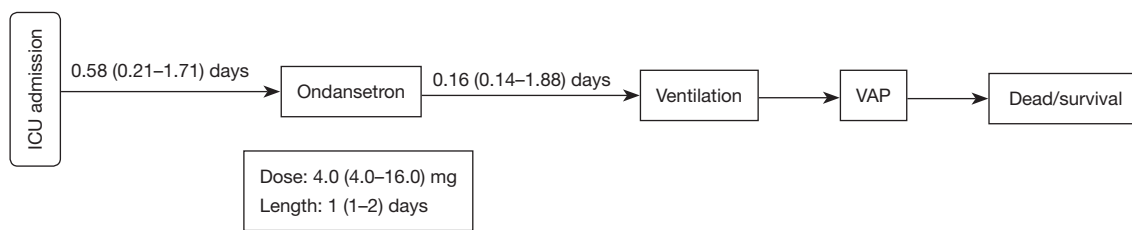
Figure 4 Dose and duration of ondansetron use. Data are presented as median (IQR). ICU, intensive care unit; VAP, ventilator-associated pneumonia; IQR, interquartile range.

need emergency intubation and ventilation have a high risk of reflux aspiration. Previous studies found that the 5-HT$_3$ receptors may mediate relaxation of rat esophageal smooth muscle (44) and esophageal motility (45), thus 5-HT$_3$ receptor antagonists might reduce the relaxation effect (44,46). Ondansetron use before ventilation may prevent reflux aspiration during the intubation process. Our study also showed that ondansetron use was associated with shorter ventilator duration. Third, 5-HT$_3$ receptor antagonists have many other effects, such as antiplatelet aggregation effect (47), reduction of cell apoptosis and oxidative stress (48) and kidney protection (49). They also affect plasma vasopressin secretion (35), have concomitant effects on autonomic nervous function (50) and inhibit sepsis by regulating the cardiac action potential (51). These mechanisms may be partly involved in reducing the mortality rate of patients on mechanical ventilation. However, the actual mechanism of the benefit for ventilated patients from ondansetron administration needs further investigation.

Several limitations should be considered. First, potential and unknown confounders may exist, as expected in all retrospective studies. However, we adjusted as many possible confounders and achieved a good balance in the PSM and IPTW cohorts in this study. Second, ondansetron is not a routine medication before mechanical ventilation, and specific indications for ondansetron administration are still unclear. However, clinically common diseases, such as malignant tumors and operation, with possible ondansetron use to prevent vomiting were analyzed in the subgroup analysis. Moreover, our results indicated that ondansetron could reduce the mortality rate of patients on mechanical ventilation in these two subgroups and other subgroups. Third, this study did not specify the amount and time of ondansetron administration, although we provided a range in the descriptive statistics (*Figure 4*). Fourth, the results reported in this study need to be further verified by further randomized trials because we obtained our data from an observational database.

Conclusions

This cohort study suggested that ondansetron use was associated with lower risk-adjusted mortality rates of patients on mechanical ventilation. 5-HT$_3$ receptor antagonist use is may be new potential adjunctive therapeutic strategy for patients on mechanical ventilation in the ICU.

Acknowledgments

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

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appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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