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Impact of initial ventilation strategies on in-hospital mortality in sepsis patients: insights from the MIMIC-IV database

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Abstract

Background This study evaluates the impact of different initial ventilation strategies on in-hospital mortality among sepsis patients.

Methods We included hospitalized sepsis patients who underwent mechanical ventilation from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database and categorized them into groups based on their initial ventilation strategy: non-invasive ventilation (NIV) and invasive mechanical ventilation (IMV). The main endpoint analyzed was in-hospital mortality. A propensity score matching model was employed to address confounding factors, and Cox survival analysis was performed in the matched cohort. Subgroup analyses were conducted to evaluate population heterogeneity.

Results Among 19,796 patients who received mechanical ventilation, 10,073 (50.8%) initially received NIV. The analysis included 2935 matched pairs. Patients initially receiving NIV exhibited a higher survival rate ($P=0.009$) and a 24% lower risk of in-hospital mortality compared to those initially receiving IMV ($P<0.001$). Subgroup analysis indicated significant survival benefits with initial NIV for patients without malignant tumor (MT), or lower Sequential Organ Failure Assessment (SOFA) scores and higher PO_2/FiO_2.

Conclusion Among sepsis patients, initial NIV is linked to increased in-hospital survival rates and reduced mortality risk, particularly in patients without concurrent MT, lower SOFA scores, and higher PO_2/FiO_2.

Keywords Sepsis, Non-invasive ventilation, Mechanical ventilation, MIMIC-IV database

Introduction

Sepsis is characterized by a dysregulated immune response by the host to infection, which can cause life-threatening organ dysfunction [1]. Sepsis also poses a major challenge within the intensive care unit (ICU), characterized by high mortality rates, significant economic burdens, and detrimental effects on many patients such as disability, functional impairment, and decreased quality of life [2–4]. Additionally, respiratory failure frequently complicates sepsis, which may exacerbate lung damage and cause respiratory dysfunction. The resulting respiratory failure manifests as lactic acidosis,

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hypoxemia, or hypercapnia, guiding the selection of initial ventilation mode [5].

Non-invasive ventilation (NIV) and invasive mechanical ventilation (IMV) serve as primary methods for respiratory management in ICUs [6]. Compared to IMV, NIV offers unique advantages, such as reducing the risks associated with intubation, and sedation. However, NIV also entails risks of discomfort related to the mask, patient-machine asynchrony, and gastric insufflation. The primary risks of NIV in acute respiratory failure (ARF) include delayed intubation and increased aspiration [7–9]. Studies suggest that unsuccessful NIV application is a significant predictor of mortality in sepsis patients, and initial ventilation strategy is linked to patient outcomes [10]. Due to the limited sample size in existing studies and the low-quality evidence, there are no clear standards for identifying sepsis patients who might benefit from NIV, and inappropriate use of NIV can be harmful. Currently, guidelines lack specific recommendations on how to choose ventilation strategies [11–13]. Nevertheless, the role of mechanical ventilation in clinical practice remains indispensable, and researching the relationship between initial ventilation strategies and sepsis outcomes is vital for improving clinical diagnosis and treatment as well as patient prognoses.

Moreover, studies suggest that NIV is only effective in patients with combined cardiopulmonary dysfunction [14]. However, opinions vary regarding its benefits for critically ill patients [15] and immunocompromised cancer patients [16–18] NIV can also potentially cause renal damage [19–21]. Exploring the association between initial ventilation strategies and outcomes in sepsis patients with varying characteristics and identifying clinical populations that may benefit from specific ventilation strategies are equally crucial.

This research, utilizing the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database, aims to explore how initial ventilation strategies impact in-hospital mortality rates in sepsis patients and reports on the outcomes among patients with different characteristics.

Materials and methods

Study design

In this retrospective cohort analysis, we drew data from the expansive MIMIC-IV database developed by the Massachusetts Institute of Technology (MIT). It includes patient care records from over 60,000 individuals admitted to the ICU at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019 [22]. The project received approval from the Institutional Review Boards at both BIDMC and MIT. Access to the database was obtained after the successful completion of the Collaborative Institutional Training Initiative program. As MIMIC-IV contained only anonymized information, patient consent was exempt.

Study population, exposure, and outcomes

We selected patients from the MIMIC-IV database diagnosed with sepsis and receiving mechanical ventilation based on the Sepsis-3.0 guidelines, which require a confirmed or suspected infection and a Sequential Organ Failure Assessment (SOFA) score of 2 or higher [1]. Individuals younger than 18 years were excluded, and only data at the initial ICU stay was considered for patients with multiple admissions. The main exposure was the strategy of initial ventilation (NIV or IMV), and in-hospital mortality was the primary endpoint.

Variable extraction

We gathered baseline data within the first 24 h of ICU admission using Structured Query Language. The extracted data included demographic and clinical details such as age, gender, weight, race, and initial assessment scores—SOFA score, Simplified Acute Physiology Score II (SAPS II), and Glasgow Coma Scale (GCS). Vital signs included mean arterial pressure (MAP), heart rate, body temperature (in Celsius), and respiratory rate. We also collected laboratory measurements like white blood cell (WBC) count, hemoglobin levels, platelet count, lactate levels, eGFR, pH, partial pressures of oxygen (pO_2), and carbon dioxide (pCO_2), PO_2/FiO_2 within the first 24 h. For repeated measures within this timeframe, the earliest recorded values were used. The eGFR was calculated using the MDRD (Modification of Diet in Renal Disease) equation: $eGFR = 186 \times (Scr - 1.154) \times (age - 0.203) \times (0.742 \text{ if female})$, where Scr denotes serum creatinine in mg/dL and age in years. The MDRD equation is validated for renal function assessment in chronic kidney disease (CKD). Data on comorbidities present at admission, such as respiratory failure, hypoxemia, hypercapnia, lactic acidosis, acute kidney failure (AKF), pneumonia, heart failure (HF), chronic kidney disease, cirrhosis, chronic obstructive pulmonary disease (COPD), stroke, and malignant tumor (MT), were also collected based on ICD-9 codes from the MIMIC-IV database. Variables with missing data exceeding 30% were excluded from analysis.

Statistical analysis

Categorical variables were presented as frequency and percentage (%). Continuous variables were reported either as means with standard deviation (SD) or medians with interquartile ranges (IQR), based on their distribution profiles. Continuous variables conforming to normal distribution were analyzed using the t-test. In contrast, those that did not follow a normal distribution, along with ordinal variables, were assessed using the Wilcoxon

rank-sum test. Analysis of categorical variables was conducted using the Chi-square test or Fisher's exact test.

Propensity score matching (PSM) was used to adjust for and equilibrate potential confounders, namely variables that were either clinically important or differed between baseline groups ($p < 0.05$) [23]. This study employed a one-to-one nearest neighbor matching, with the caliper width at 0.05. The effectiveness of PSM was evaluated by calculating the standardized mean differences (SMDs). Despite adjusting for measured confounders, PSM cannot account for unmeasured confounding factors. For the matched cohort, Kaplan-Meier (KM) survival curves and multivariable Cox proportional hazards models were utilized to report hazard ratios (HRs) and 95% confidence intervals (CIs) concerning the initial ventilation strategies and their outcomes. Confounders that remained significant post-matching were included in the multivariable Cox analysis. Furthermore, subgroup analyses were performed by splitting the matched population into different subgroups based on the presence of age, gender, HF, COPD, MT, AKF, CKD, cause of respiratory failure, and median of the PaO_2/FiO_2, quartiles of the SOFA score. Forest plots were used to report differences in the impact of NIV on mortality risk across different populations.

Data management and statistical analysis were conducted using R (v 4.4.0), with significance set at $p < 0.05$.

Results

Patient characteristics and outcomes before matching

An analysis of 23,316 sepsis patients revealed that 19,796 of them received mechanical ventilation. Of these, 10,073 (50.9%) initially received NIV, and 9,723 (49.1%) received IMV. On average, the included population was 67 years old (± 16.05), with a higher proportion of males (58.6%), and most being white(77.2%). The overall SOFA score was 5 (3,7); the SAPS II score was 38 (31,48). Compared to patients initially receiving IMV, those treated with NIV were older (68.54 ± 16.20), lighter in weight (81.82 ± 24.03), and had less severe illness as indicated by lower SOFA scores (5(3,7)) and SAPS II scores (37(29,46)) and GCS scores (14(13,15)), higher pH levels (7.37 ± 0.07), and lower serum lactate levels (2.14 ± 1.44). The IMV group demonstrated higher eGFR (79.33 ± 47.10) and PIO2/FIO2 (411.8 ± 259.3). Regarding comorbidities, compared to the IMV group, NIV patients showed an increased prevalence of HF (32.66% vs. 24.47%), COPD (8.84% vs. 6.35%), CKD(20.50% vs. 14.95%), AKF(42.85% vs. 32.39%), MT(18.27% vs. 13.94%), and hypoxemia (12.78% vs. 10.81%), while stroke(8.74% vs. 9.48%), hypercapnia (2.71% vs. 2.5%), and lactic acidosis (19.50% vs. 18.99%) rates remained similar between groups. There were no statistically significant differences in vital signs within 24 h of admission between the groups (Table 1).

In the unmatched cohort, the overall in-hospital mortality rate stood at 14.6% (2884/19796). 12.7% (1276/10073) of patients treated with NIV and 16.5% (1608/9723) of patients treated with IMV died in hospital. The incidence of switching from NIV to IMV was 23.1% (2328/10073), and among these patients, the in-hospital mortality was recorded at 20.1% (469/2328).

Characteristics and outcomes of patients after matching

After matching, 2935 pairs of patients initially treated with NIV (% of the initial NIV cohort) and those treated with IMV were included. Post-matching, the imbalance in covariates as measured by the SMD significantly decreased, indicating effective matching. No difference in respiratory rate and SPO_2 was observed between the groups before matching; after matching, the NIV group exhibited a lower respiratory rate (19.88 ± 4.20) with a significant difference (SMD: 0.192, $P < 0.001$) and a lower Spo2 (96.88 ± 2.44) with a significant difference (SMD:0.368, $P < 0.001$). After matching, the SAPS II score (42.10 ± 14.61; SMD: 0.054; $P = 0.031$) differed between groups (Table 2).

The overall mortality rate among the matched patients was 15.8% (928/5870), and the NIV group experienced a lower in-hospital mortality rate of 15.1% (444/2935) compared to 16.5% (484/2935) in the IMV group. The incidence of switching from NIV to IMV post-matching was 35% (1029/2935), with an in-hospital mortality rate of 21.1% (218/1029) observed in this group.

KM curves and survival analysis

In the analysis of matched samples, the KM survival estimates demonstrated a notable disparity in survival between patients initially treated with NIV and those with IMV. The survival rate was notably higher in the initial NIV group ($P = 0.009$) (Fig. 1). Further analysis using a multivariable Cox proportional hazards model confirmed that the initial ventilation strategy significantly impacted in-hospital mortality in sepsis patients. Specifically, those initially treated with NIV exhibited a 24% reduction in the risk of in-hospital death compared to those receiving IMV (HR: 0.76, 95% CI: 0.67–0.87, $P < 0.001$) (Table 3).

Subgroup analysis

Subgroup analyses stratified by gender, age, HF, COPD, malignancy, CKD, AKF, hypoxemia, hypercapnia, lactic acidosis, SOFA score, and oxygenation index evaluated the association between initial ventilation mode and hospital mortality. The hazard ratios (HR) for in-hospital mortality were significantly different in subgroups younger than 67 years and subgroups of men ($P < 0.05$). However, there were no statistical differences in subgroups older than 67 years and women ($P > 0.05$). The association between initial ventilation pattern and

Table 1 Baseline characteristics in the original cohort

Variables	Total (*n* = 19796)	IMV (*n* = 9723)	NIV (*n* = 10073)	Statistic	*P*
Age	66.81 ± 16.05	65.01 ± 15.69	68.54 ± 16.20	t=-15.59	**< 0.001**
Gender, n(%)				χ^2=118.68	**< 0.001**
F	8204 (41.44)	3652 (37.56)	4552 (45.19)		
M	11,592 (58.56)	6071 (62.44)	5521 (54.81)		
Race, n(%)				χ^2=36.34	**< 0.001**
Black	1485 (8.56)	638 (7.74)	847 (9.31)		
Other	2471 (14.25)	1294 (15.70)	1177 (12.94)		
White	13,384 (77.19)	6312 (76.56)	7072 (77.75)		
Weigh	83.69 ± 23.94	85.61 ± 23.69	81.82 ± 24.03	t = 11.12	**< 0.001**
Laboratory Tests					
WBC (× 10^9/L)	13.33 ± 10.24	13.60 ± 10.78	13.06 ± 9.68	t = 3.67	**< 0.001**
Platelet (× 10^{12}/L)	196.37 ± 104.20	188.55 ± 95.76	203.96 ± 111.27	t=-10.42	**< 0.001**
Hemoglobin (× 10^9/L)	10.52 ± 1.89	10.57 ± 1.82	10.48 ± 1.95	t = 3.19	**0.001**
PH	7.37 ± 0.07	7.36 ± 0.07	7.37 ± 0.07	t=-8.60	**< 0.001**
pCO2 (mmHg)	41.74 ± 9.34	41.56 ± 8.35	41.98 ± 10.50	t=-2.71	**0.007**
pO2 (mmHg)	151.20 ± 83.55	174.63 ± 81.31	120.14 ± 76.02	t = 43.99	**< 0.001**
PO_2/FiO_2	363.79 ± 256.12	411.82 ± 259.32	275.31 ± 224.70	t = 33.24	**< 0.001**
Lactate l (mmol/L)	2.32 ± 1.78	2.48 ± 2.01	2.14 ± 1.44	t = 12.52	**< 0.001**
Ureanitrogen (mg/dL)	27.45 ± 21.37	25.06 ± 19.80	29.76 ± 22.55	t=-15.55	**< 0.001**
Creatinine(mg/dL)	1.46 ± 1.42	1.34 ± 1.22	1.58 ± 1.57	t=-11.85	**< 0.001**
eGFR	74.47 ± 46.04	79.33 ± 47.10	69.77 ± 44.49	t = 14.65	**< 0.001**
Vital Signs					
MAP (mmHg)	80.47 ± 612.21	85.31 ± 908.87	76.47 ± 51.70	t = 0.95	0.344
Respiratory rate (bpm)	24.19 ± 644.61	28.30 ± 919.90	20.21 ± 4.29	t = 0.88	0.378
Spo2(%)	99.82 ± 301.94	99.26 ± 164.73	100.35 ± 391.12	t=-0.25	0.799
Temperature (°C)	36.84 ± 1.89	36.83 ± 2.59	36.85 ± 1.04	t=-0.87	0.386
Disease Severity Score					
GCS	15.00 (13.00, 15.00)	15.00 (14.00, 15.00)	14.00 (13.00, 15.00)	Z=-14.84	**< 0.001**
SAPS II score	38.00 (31.00, 48.00)	40.00 (32.00, 51.00)	37.00 (29.00, 46.00)	Z=-20.32	**< 0.001**
SOFA score	5.00 (3.00, 8.00)	6.00 (4.00, 9.00)	5.00 (3.00, 7.00)	Z=-24.01	**< 0.001**
Comorbidities					
HF				χ^2=162.54	**< 0.001**
No	14,127 (71.36)	7344 (75.53)	6783 (67.34)		
Yes	5669 (28.64)	2379 (24.47)	3290 (32.66)		
MT				χ^2=68.55	**< 0.001**
No	16,601 (83.86)	8368 (86.06)	8233 (81.73)		
Yes	3195 (16.14)	1355 (13.94)	1840 (18.27)		
CKD				χ^2=104.12	**< 0.001**
No	16,277 (82.22)	8269 (85.05)	8008 (79.50)		
Yes	3519 (17.78)	1454 (14.95)	2065 (20.50)		
AKF				χ^2=230.45	**< 0.001**
No	12,331 (62.29)	6574 (67.61)	5757 (57.15)		
Yes	7465 (37.71)	3149 (32.39)	4316 (42.85)		
Stroke				χ^2=3.33	0.068
No	17,994 (90.90)	8801 (90.52)	9193 (91.26)		
Yes	1802 (9.10)	922 (9.48)	880 (8.74)		
COPD				χ^2=43.60	**< 0.001**
No	18,289 (92.39)	9106 (93.65)	9183 (91.16)		
Yes	1507 (7.61)	617 (6.35)	890 (8.84)		
Respiratory failure, n (%)				χ^2=144.99	**< 0.001**
No	12,325 (62.26)	5643 (58.04)	6682 (66.34)		
Yes	7471 (37.74)	4080 (41.96)	3391 (33.66)		
Hypoxemia, n (%)				χ^2=18.38	**< 0.001**

Table 1 (continued)

Variables	Total (*n* = 19796)	IMV (*n* = 9723)	NIV (*n* = 10073)	Statistic	*P*
No	17,458 (88.19)	8672 (89.19)	8786 (87.22)		
Yes	2338 (11.81)	1051 (10.81)	1287 (12.78)		
Hypercapnia, n (%)				χ^2=0.87	0.352
No	19,280 (97.39)	9480 (97.50)	9800 (97.29)		
Yes	516 (2.61)	243 (2.50)	273 (2.71)		
Lactic acidosis, n (%)				χ^2=0.83	0.361
No	15,986 (80.75)	7877 (81.01)	8109 (80.50)		
Yes	3810 (19.25)	1846 (18.99)	1964 (19.50)		

WBC white blood cell, MAP mean arterial pressure, PO2 partial pressure of oxygen, PCO2 partial pressure of carbon dioxide, FiO_2 Fraction of Inspired Oxygen, GCS Glasgow coma score, SAPS II Simplified Acute Physiology Score II, SOFA Sequential Organ Failure Assessment, HF heart failure, MT Malignant tumor, COPD chronic obstructive pulmonary disease, CKD chronic kidney disease, AKF acute kidney failure

in-hospital mortality was statistically significant regardless of HF ($P<0.05$). In contrast, HR values for in-hospital mortality were statistically significant only in patients without MT, CKD, AKF, or COPD ($P<0.05$). In addition, in the subgroup grouped by respiratory failure etiology, HR for in-hospital mortality was significant only in the subgroup without hypoxemia, hypercapnia, and lactic acidosis($P<0.05$). Finally, for patients with SOFA scores less than 4 and oxygenation index ≥ 241, there was a statistically significant association between initial ventilation mode and in-hospital mortality. ($P<0.05$)

The interaction analysis showed that in subgroups based on gender, HF, COPD, CKD, AKF, hypoxemia, hypercapnia, or lactic acidosis, the initial ventilation mode had no significant impact on mortality risk ($P>0.05$). However, in subgroups based on age, MT, SOFA score, and PO2/FiO2, NIV was significantly associated with a reduced mortality risk compared to IMV ($P<0.05$). Particularly, NIV was closely associated with a lower mortality risk in patients with no MT 、lower SOFA scores, and higher PO2/FiO2. In contrast, in patients with MT、 higher SOFA scores, and lower PO2/FiO2, the difference in mortality risk between NIV and IMV disappeared, suggesting that other factors, aside from the initial ventilation mode, may influence the outcomes in these subgroups (Tables 4 and 5; Figs. 2 and 3).

Discussion

Among approximately 20,000 sepsis patients who received mechanical ventilation included in this retrospective analysis, nearly half were initially treated with NIV. These patients had milder conditions upon admission, lower SOFA scores, and a higher prevalence of COPD and HF. Following PSM, the survival analysis highlighted a decreased mortality risk in patients who started with NIV rather than IMV, especially among patients without MT, or lower SOFA scores, and higher PO2/FiO2.

The benefit of using NIV to treat sepsis patients remains controversial, and most mechanical ventilation recommendations for sepsis patients are derived from Acute Respiratory Distress Syndrome (ARDS) trials. The LUNG SAFE study, which included 2,813 patients with ARDS, indicated that 15% of ARDS patients used NIV, with varying rates of failure and mortality based on ARDS severity [15]. Ferrer et al. found that NIV not only decreased the need for intubation but also reduced occurrences of septic shock and ICU mortality when compared to high-concentration oxygen therapy in cases of severe acute hypoxemic respiratory failure (AHRF) [24]. Similarly, a multicenter randomized controlled trial (RCT) involving 40 patients with acute lung injury demonstrated lower intubation rates and mortality for those treated with NIV versus those receiving oxygen therapy alone [25]. Honrubia et al. observed that while NIV did not significantly reduce mortality rates compared to IMV in patients with ARF, it did lead to fewer intubations and complications [26]. Antonelli et al. demonstrated that NIV was comparable to invasive methods in enhancing gas exchange for patients with AHRF and could avoid endotracheal intubation and reduce the occurrence of ventilator-associated pneumonia [27]. A retrospective examination of pneumonia patients revealed that initial use of NIV was significantly associated with higher hospitalization survival in comparison to IMV but was only applicable to patients with cardiopulmonary diseases, and patients for whom NIV failed had a high in-hospital mortality rate [14]. The reasons behind this association may be that NIV is typically used at an earlier stage of disease intervention and control, helping to reduce complications, promote patient recovery, and facilitate early activity. These constitute the advantages of NIV in the management of sepsis [28]. The use of NIV may imply an earlier intervention in respiratory support, especially before patients reach the severe respiratory failure stage requiring IMV. This early intervention could help control the condition more quickly, prevent further deterioration, and thus reduce the mortality risk [29, 30]. Mechanical ventilation supports breathing and gas exchange, either partially or fully, with the primary aim of maintaining adequate alveolar ventilation and arterial oxygen levels, thus preventing respiratory acidosis and hypoxemia

Table 2 Baseline characteristics in the matched cohort

Variable	Matched cohort					
	Total (*n* = 5870)	**IMV (*n* = 2935)**	**NIV (*n* = 2935)**	**Statistic**	***P***	**SMD**
Age	65.76 ± 15.73	66.08 ± 15.46	65.44 ± 15.98	t = 1.545	0.122	-0.040
Gender, n (%)				χ^2=0.178	0.673	
F	2494 (42.49)	1255 (42.76)	1239 (42.21)			-0.011
M	3376 (57.51)	1680 (57.24)	1696 (57.79)			0.011
Race, n (%)				χ^2=0.763	0.683	
Black	521 (8.88)	264 (8.99)	257 (8.76)			-0.008
Other	865 (14.74)	421 (14.34)	444 (15.13)			0.022
White	4484 (76.39)	2250 (76.66)	2234 (76.12)			-0.013
Weigh	84.68 ± 24.96	84.34 ± 24.28	85.02 ± 25.62	t=-1.044	0.297	0.027
Laboratory Tests						
WBC (× 10^9/L)	13.67 ± 9.79	13.69 ± 10.82	13.64 ± 8.64	t = 0.222	0.824	-0.007
Platelet (× 10^{12}/L)	203.03 ± 111.01	203.15 ± 103.72	202.91 ± 117.86	t = 0.083	0.934	-0.002
Hemoglobin (× 10^9/L)	10.48 ± 1.90	10.47 ± 1.89	10.49 ± 1.91	t=-0.279	0.780	0.007
PH	7.36 ± 0.07	7.36 ± 0.07	7.36 ± 0.08	t=-0.213	0.831	0.005
pCO2 (mmHg)	42.25 ± 9.99	42.11 ± 9.35	42.40 ± 10.59	t=-1.111	0.267	0.027
pO2 (mmHg)	139.60 ± 74.03	139.71 ± 71.67	139.50 ± 76.34	t = 0.105	0.916	-0.003
Lactate level (mmol/L)	2.21 ± 1.64	2.23 ± 1.73	2.19 ± 1.54	t = 0.866	0.386	-0.024
Ureanitrogen (mg/dL)	28.71 ± 22.20	28.92 ± 22.64	28.51 ± 21.76	t = 0.692	0.489	-0.018
Creatinine (mg/dL)	1.49 ± 1.36	1.49 ± 1.39	1.49 ± 1.32	t=-0.056	0.955	0.002
eGFR	73.56 ± 45.30	73.06 ± 42.60	74.05 ± 47.84	t=-0.837	0.403	0.021
Vital Signs						
MAP (mmHg)	75.55 ± 65.04	74.66 ± 11.20	76.44 ± 91.30	t=-1.049	0.294	0.020
Respiratory rate (bpm)	19.88 ± 4.20	19.45 ± 3.88	20.31 ± 4.45	t=-7.843	**< 0.001**	0.192
Spo2(%)	97.01 ± 4.35	97.42 ± 5.71	96.60 ± 2.22	t = 7.234	**< 0.001**	-0.368
Temperature (°C)	36.82 ± 2.19	36.80 ± 2.78	36.84 ± 1.37	t=-0.675	0.500	0.028
Disease Severity Score						
GCS	13.27 ± 3.12	13.26 ± 3.29	13.28 ± 2.95	t=-0.292	0.770	0.008
SAPS II score	42.10 ± 14.61	42.51 ± 14.05	41.69 ± 15.15	t = 2.159	**0.031**	-0.054
SOFA score	6.44 ± 3.66	6.48 ± 3.64	6.39 ± 3.67	t = 0.978	0.328	-0.025
Comorbidities						
HF				χ^2=2.389	0.122	
No	4243 (72.28)	2095 (71.38)	2148 (73.19)			0.041
Yes	1627 (27.72)	840 (28.62)	787 (26.81)			-0.041
MT				χ^2=0.101	0.750	
No	4915 (83.73)	2462 (83.88)	2453 (83.58)			-0.008
Yes	955 (16.27)	473 (16.12)	482 (16.42)			0.008
CKD				χ^2=0.234	0.629	
No	4856 (82.73)	2421 (82.49)	2435 (82.96)			0.013
Yes	1014 (17.27)	514 (17.51)	500 (17.04)			-0.013
AKF				χ^2=0.227	0.634	
No	3416 (58.19)	1699 (57.89)	1717 (58.50)			0.012
Yes	2454 (41.81)	1236 (42.11)	1218 (41.50)			-0.012
Stroke				χ^2=0.396	0.529	
No	5407 (92.11)	2710 (92.33)	2697 (91.89)			-0.016
Yes	463 (7.89)	225 (7.67)	238 (8.11)			0.016
COPD				χ^2=0.244	0.621	
No	5323 (90.68)	2656 (90.49)	2667 (90.87)			0.013
Yes	547 (9.32)	279 (9.51)	268 (9.13)			-0.013
Respiratory failure, n (%)				χ^2=0.573	0.449	
No	2963 (50.48)	1467 (49.98)	1496 (50.97)			0.020
Yes	2907 (49.52)	1468 (50.02)	1439 (49.03)			-0.020
Hypoxemia, n (%)				χ^2=0.166	0.684	

Table 2 (continued)

Variable	Matched cohort					
	Total (*n* = 5870)	**IMV (*n* = 2935)**	**NIV (*n* = 2935)**	**Statistic**	***P***	**SMD**
No	5015 (85.43)	2502 (85.25)	2513 (85.62)			0.011
Yes	855 (14.57)	433 (14.75)	422 (14.38)			-0.011
Hypercapnia, n (%)				χ^2=0.172	0.679	
No	5652 (96.29)	2829 (96.39)	2823 (96.18)			-0.011
Yes	218 (3.71)	106 (3.61)	112 (3.82)			0.011
Lactic acidosis, n (%)				χ^2=0.001	0.975	
No	4527 (77.12)	2263 (77.10)	2264 (77.14)			0.001
Yes	1343 (22.88)	672 (22.90)	671 (22.86)			-0.001

WBC white blood cell, MAP mean arterial pressure, PO2 partial pressure of oxygen, PCO2 partial pressure of carbon dioxide, GCS Glasgow coma score, SAPS II Simplified Acute Physiology Score II, SOFA Sequential Organ Failure Assessment, HF heart failure, MT Malignant tumor, COPD chronic obstructive pulmonary disease, CKD chronic kidney disease, AKF acute kidney failure

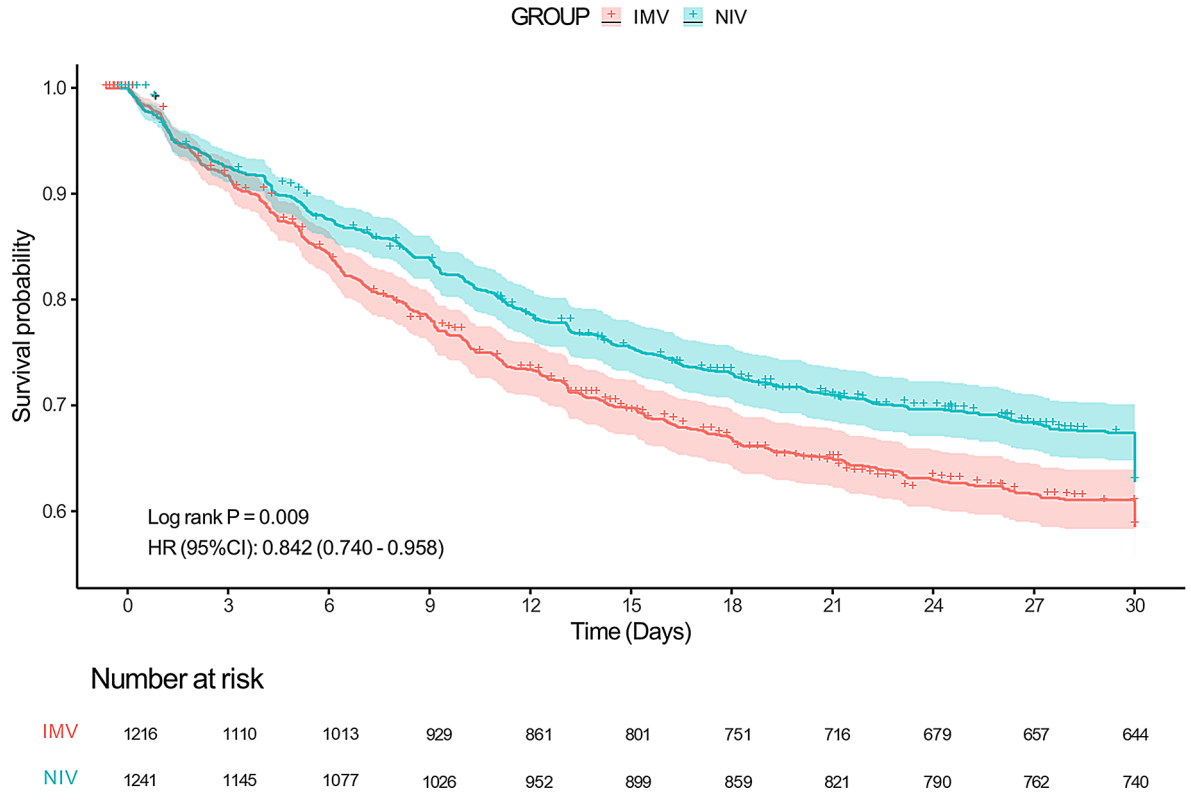

Fig. 1 Kaplan-Meier survival analysis curve for the in-hospital mortality of matched cohort. HR: Hazard Ratio, CI: Confidence Interval

Table 3 Multifactor Cox proportional hazards model in the matched cohort

Variables	β	S.E	Z	*P*	HR (95%CI)
Group					
IMV					1.00 (Reference)
NIV	-0.27	0.07	-4.14	**< 0.001**	0.76 (0.67 ~ 0.87)
Respiratory rate (bpm)	0.06	0.01	7.44	**< 0.001**	1.06 (1.04 ~ 1.08)
Spo2(%)	-0.08	0.01	-9.91	**< 0.001**	0.92 (0.91 ~ 0.94)
SAPS II	0.03	0.00	13.11	**< 0.001**	1.03 (1.02 ~ 1.03)

HR: Hazard Ratio, CI: Confidence Interval

[9]. Compared to IMV, NIV appears to cause less interference with airway protection and defense [31]. Patients on IMV often require sedatives and muscle relaxants to aid ventilation, which can suppress their ability to breathe autonomously and cough, thereby increasing the risk of pneumonia and other complications [32, 33]. In contrast, patients on NIV retain some ability to breathe autonomously and expectorate, reducing the occurrence of complications. Patients using NIV, by avoiding endotracheal intubation and the discomfort and restrictions associated with mechanical ventilation, may engage more readily in early activity and rehabilitation exercises. These activities help improve the patient's cardiopulmonary

Table 4 Subgroup analysis of initial ventilation mode based on demographics and comorbidities in sepsis patients

Variables	*n* (%)	IMV	NIV	HR (95%CI)	*P*	*P* for interaction
All patients	5870 (100.00)	484/2935	444/2935	0.80 (0.71 ~ 0.92)	**0.001**	
Gender						0.007
F	2494 (42.49)	212/1255	222/1239	0.97 (0.80 ~ 1.18)	0.772	
M	3376 (57.51)	272/1680	222/1696	0.69 (0.57 ~ 0.82)	**< 0.001**	
Age						0.218
<67	2818 (48.01)	177/1382	147/1436	0.71 (0.57 ~ 0.89)	**0.002**	
≥67	3052 (51.99)	307/1553	297/1499	0.85 (0.72 ~ 1.00)	**0.047**	
HF						0.649
No	4243 (72.28)	313/2095	298/2148	0.81 (0.69 ~ 0.95)	**0.011**	
Yes	1627 (27.72)	171/840	146/787	0.77 (0.61 ~ 0.96)	**0.021**	
MT						0.027
No	4915 (83.73)	384/2462	330/2453	0.75 (0.65 ~ 0.87)	**< 0.001**	
Yes	955 (16.27)	100/473	114/482	1.01 (0.76 ~ 1.34)	0.949	
CKD						0.695
No	4856 (82.73)	373/2421	339/2435	0.79 (0.68 ~ 0.92)	**0.002**	
Yes	1014 (17.27)	111/514	105/500	0.86 (0.65 ~ 1.14)	0.299	
AKF						0.097
No	3416 (58.19)	166/1699	147/1717	0.71 (0.56 ~ 0.89)	**0.003**	
Yes	2454 (41.81)	318/1236	297/1218	0.87 (0.74 ~ 1.02)	0.090	
COPD						0.717
No	5323 (90.68)	432/2656	398/2667	0.80 (0.70 ~ 0.92)	**0.002**	
Yes	547 (9.32)	52/279	46/268	0.90 (0.59 ~ 1.36)	0.613	

HR: Hazard Ratio, CI: Confidence Interval, HF heart failure, MT Malignant tumor, COPD chronic obstructive pulmonary disease, CKD chronic kidney disease, AKF acute kidney failure

Table 5 Subgroup analysis of initial ventilation mode based on oxygenation and disease severity in sepsis patients

Variables	*n* (%)	IMV	NIV	HR (95%CI)	*P*	*P* for interaction
All patients	5870 (100.00)	484/2935	444/2935	0.80 (0.71 ~ 0.92)	**0.001**	
hypoxemia						0.818
No	5015 (85.43)	379/2502	357/2513	0.82 (0.71 ~ 0.95)	**0.009**	
Yes	855 (14.57)	105/433	87/422	0.79 (0.58 ~ 1.05)	0.108	
hypercapnia						0.781
No	5652 (96.29)	459/2829	413/2823	0.80 (0.70 ~ 0.92)	**0.001**	
Yes	218 (3.71)	25/106	31/112	0.70 (0.38 ~ 1.29)	0.253	
lactic acidosis						0.371
No	4527 (77.12)	297/2263	281/2264	0.78 (0.66 ~ 0.92)	**0.003**	
Yes	1343 (22.88)	187/672	163/671	0.89 (0.72 ~ 1.11)	0.304	
SOFA						0.001
Q1	1327 (22.61)	59/652	31/675	0.41 (0.27 ~ 0.64)	**< 0.001**	
Q2	1405 (23.94)	62/677	69/728	0.81 (0.57 ~ 1.15)	0.236	
Q3	1575 (26.83)	123/802	132/773	0.79 (0.61 ~ 1.02)	0.076	
Q4	1563 (26.63)	240/804	212/759	1.03 (0.85 ~ 1.25)	0.750	
PO_2/FiO_2						0.007
<241	2567 (49.99)	301/1353	275/1214	1.00 (0.84 ~ 1.18)	0.953	
≥241	2568 (50.01)	182/1569	87/999	0.66 (0.51 ~ 0.86)	**0.002**	

HR: Hazard Ratio, CI: Confidence Interval, SOFA Sequential Organ Failure Assessment, PO2 partial pressure of oxygen, FiO_2 Fraction of Inspired Oxygen, SOFA quartile Q1:<4; Q2:4–5; Q3:6–8; Q4:≥9

function, muscle strength, and overall health status, thereby accelerating the recovery process and decreasing mortality risk [34, 35]. Furthermore, by avoiding invasive procedures such as tracheal intubation, NIV lowers the risk of discomfort and delirium by maintaining patient alertness and interaction with their surroundings, which enhances treatment compliance and rehabilitation outcomes, thus lowering mortality [36].

Additionally, some studies report inconsistent conclusions. In research focused on initial ventilation strategy choices for older patients with pneumonia, compared to IMV, using NIV as the initial strategy did not result in

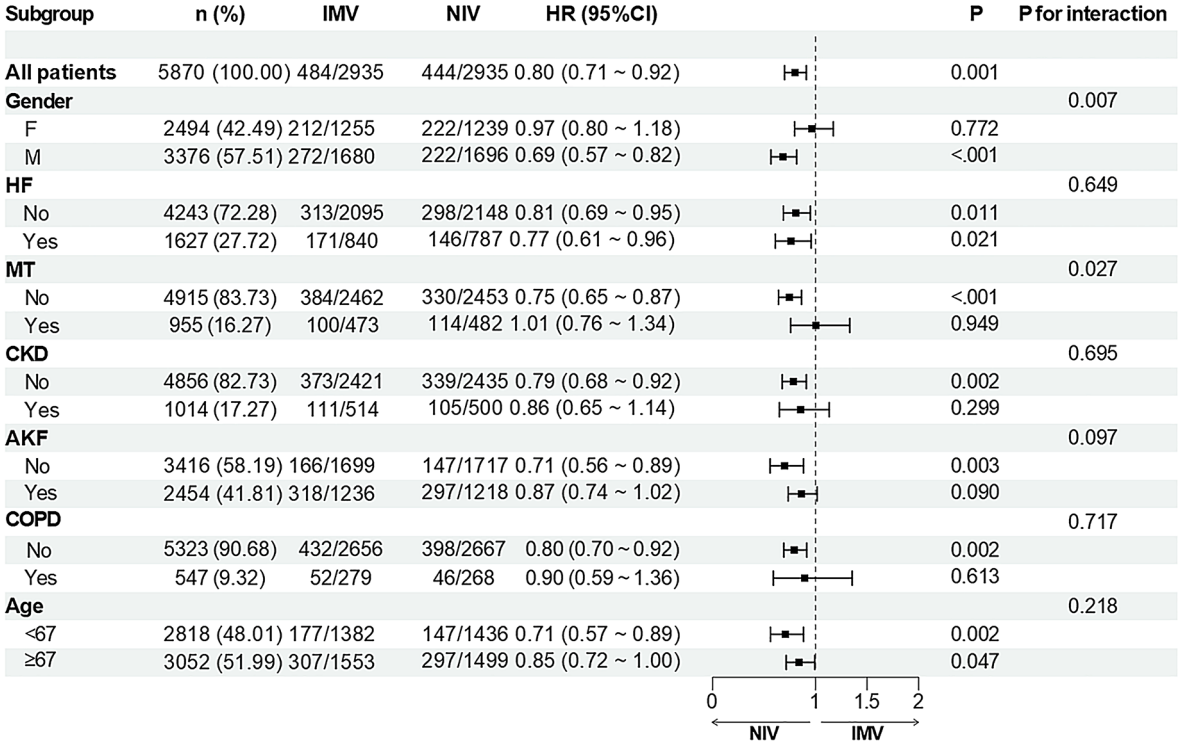

Fig. 2 Forest plot of HRs for the primary endpoint in different subgroups of the matched cohort. HR: Hazard Ratio, CI: Confidence Interval, HF heart failure, MT Malignant tumor, COPD chronic obstructive pulmonary disease, CKD chronic kidney disease, AKF acute kidney failure, NIV non-invasive ventilation, invasive mechanical ventilation IMV

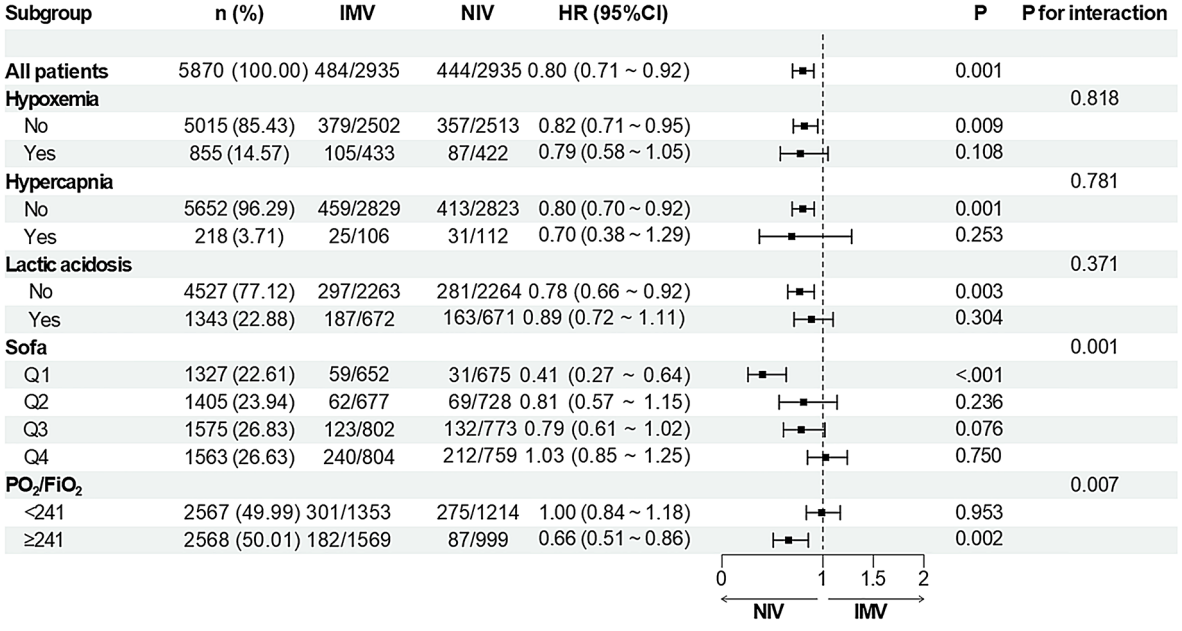

Fig. 3 Forest plot of HRs for the primary endpoint in different subgroups of the matched cohort. HR: Hazard Ratio, CI: Confidence Interval, SOFA Sequential Organ Failure Assessment, PO2 partial pressure of oxygen, FiO_2 Fraction of Inspired Oxygen, SOFA quartile Q1:<4; Q2:4–5; Q3:6–8; Q4:≥9, NIV non-invasive ventilation, invasive mechanical ventilation IMV

lower in-hospital mortality rates; there was no clear harm signal from using NIV, but researchers suggest that NIV should be cautiously selected for such patients [37, 38]. Moreover, He et al. found that compared to standard oxygen therapy, while NIV treatment could improve the oxygenation index (PaO2/FIO2), it failed to decrease intubation rates in patients with early mild ARDS caused by pneumonia [39]. This inconsistency in studies may relate to the risk of lung injury exacerbated by NIV treatment in ARDS, where increased intrapulmonary pressure and promotion of inflammation are primary causes of damage [40]. Inappropriate use of NIV may adversely affect patient outcomes [41].

This study observed that sepsis patients initially treated with NIV exhibited higher in-hospital survival rates and lower mortality risk compared to those initially treated with IMV. This aligns with the experimental conclusions reported by Antonelli and Stefan et al. However, Valley et al. and Besen et al. did not observe such benefits, which might be attributed to several factors: First, our analysis included all ventilated sepsis patients rather than only older patients with pneumonia. Second, the experiments by Valley et al. excluded patients with COPD or HF, whereas our study did not exclude such patients, and the proportion of patients with these comorbidities was not high. Third, our findings focus on in-hospital mortality instead of 30-day mortality. Fourth, patients with severe conditions who were late in receiving restrictive intubation tended to be treated with NIV and died after discharge. Additionally, sepsis-induced respiratory failure manifests as hypoxemia, hypercapnia, or lactic acidosis, each requiring specific ventilation strategies. Prior studies lacked stratification by respiratory failure type, limiting ventilation mode selection guidance. Data extraction and matching in this study minimized the impact of this heterogeneity. It is noteworthy that while Stefan and Besen et al. believed the benefits of initial NIV might be due to comorbid cardiopulmonary diseases, our adjusted cohort subgroup analysis did not observe differences in survival benefits between subgroups with or without COPD or HF, possibly due to the inefficiency of subgroup analyses and the relatively few patients with HF or COPD in the matched cohort. Additionally, compared to IMV, initial NIV was linked to a decreased mortality risk only in patients without MT, possibly because patients with sepsis and concurrent MT have compromised immunity, a higher probability of NIV failure, and a poorer prognosis [42]. Differences in risk ratios were also observed in patients with different PO_2/FiO_2. The decrease in mortality risk with NIV in higher PO_2/FiO_2 patients was statistically significant [20]. In patients with lower oxygenation indices, disease severity, and subsequent NIV failure contributed to increased mortality risk. Furthermore, in different SOFA score subgroups, we observed that high SOFA scores were associated with nonsignificant survival benefits, and in patients with SOFA scores ≥ 4, no link was found between initial NIV and survival benefits, possibly due to increased rates of NIV failure, more aggressive and prolonged ventilator support, delayed intubation, and poorer prognosis in severely ill patients. This finding is consistent with previous studies [43, 44]. However, due to the inefficiency of subgroup analysis, further RCTs are needed to verify the relationship between initial ventilation strategy choices and outcomes in different sepsis populations.

Our study has several strengths. This study utilized a rich electronic medical record database with a sufficient sample size, enabling adjustments for disease severity at admission using validated indicators, including laboratory test results. Furthermore, PSM was utilized to adjust for multiple confounding factors. However, there are notable limitations. Firstly, it is a single-center retrospective study predominantly involving a Caucasian population, and its conclusions may not be applicable to other populations. Secondly, data collection through SQL queries limited data completeness and accuracy, introducing potential selection bias despite quality control measures. Thirdly, while PSM adjusted for multiple known confounders in this retrospective study, unmeasured factors remained potential confounders. Additionally, since this study is based on electronic medical records from routine clinical visits, there is an inherent risk of measurement errors in the indicators used. Fourthly, many clinical decisions, including patient symptoms and physician experience, are not recorded in electronic records, introducing potential bias - evidenced by the 35% NIV-to-IMV conversion rate. Lastly, our study only assessed the impact of the initial ventilation strategy on in-hospital mortality among sepsis patients; the broader effects of NIV on the prognosis of sepsis need to be validated by more comprehensive research. Future large-scale RCTs are still needed to further verify the relationship between NIV and sepsis.

Conclusion

In summary, in patients with sepsis, initial NIV compared to IMV is linked to elevated survival rates and a decreased risk of mortality, particularly in patients without MT, and those with higher PO_2/FiO_2 and a SOFA score of less than 4.

Abbreviations

MIMIC-IV	Medical information mart for intensive care IV
NIV	Non-invasive ventilation
IMV	Invasive mechanical ventilation
MT	Malignant tumor
SOFA	Sequential organ failure assessment
ICU	Intensive care unit
ARF	Acute respiratory failure
BIDMC	Beth israel deaconess medical center
SAPS II	Simplified acute physiology score II
GCS	Glasgow coma scale

MAP	Vital signs included mean arterial pressure
in Celsius	Heart rate; body temperature
AKF	Admission, such as acute kidney failure
HF	Heart failure
CKD	Chronic kidney disease
COPD	Cirrhosis, chronic obstructive pulmonary disease
FiO_2	Fraction of inspired oxygen
eGFR	Estimated glomerular filtration rate

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Author contributions
All authors contributed to the study conception and design. Writing - original draft preparation: [YL]; Writing - review and editing: [LS, JZ, WZ]; Conceptualization: [YL, LS, JZ, WZ]; Methodology: [YL, JZ, WZ, HS]; Formal analysis and investigation: [YL, KW, ZL, HS]; Funding acquisition: [LS]; Resources: [LS]; Supervision: [LS], and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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