The Impact of Delayed Transition From Noninvasive to Invasive Mechanical Ventilation on Hospital Mortality in Immunocompromised Patients With Sepsis

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OBJECTIVE: To determine whether mortality differed between initial invasive mechanical ventilation (IMV) or noninvasive ventilation (NIV) followed by delayed IMV in immunocompromised patients with sepsis.

DESIGN: Retrospective analysis using the National Data Center for Medical Service claims data in China from 2017 to 2019.

SETTING: A total of 3530 hospitals across China.

PATIENTS: A total of 36,187 adult immunocompromised patients with sepsis requiring ventilation.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was hospital mortality. Patients were categorized into NIV initiation or IMV initiation groups based on first ventilation. NIV patients were further divided by time to IMV transition: no transition, immediate (≤ 1 d), early (2–3 d), delayed (4–7 d), or late (≥ 8 d). Mortality was compared between groups using weighted Cox models. Over the median 9-day follow-up, mortality was similar for initial NIV versus IMV (adjusted hazard ratio [HR] 1.006; 95% CI, 0.959–1.055). However, among NIV patients, a longer time to IMV transition is associated with stepwise increases in mortality, from immediate transition (HR 1.65) to late transition (HR 2.51), compared with initial IMV. This dose-response relationship persisted across subgroups and sensitivity analyses.

CONCLUSIONS: Prolonged NIV trial before delayed IMV transition is associated with higher mortality in immunocompromised sepsis patients ultimately intubated.

KEYWORDS: immunocompromised; mechanical ventilation; mortality; noninvasive ventilation; sepsis

BACKGROUND

The increasing availability of new therapeutic strategies for malignancy, autoimmune conditions, and organ transplantations has led to an increase in the number of immunocompromised critically ill patients, most of whom require ventilatory support (1, 2). Invasive mechanical ventilation (IMV) has been linked to a high mortality rate among immunocompromised patients (3), whereas noninvasive ventilation (NIV) can mitigate the need for endotracheal intubation by reducing the work of breathing and enhancing gas exchange. However, with the substantially decreased mortality of immunocompromised patients with respiratory failure, current data do not support a ventilatory strategy different from that for nonimmunocompromised patients (3). Nevertheless, the most recent

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KEY POINTS

Question: Whether mortality differ between initial invasive mechanical ventilation (IMV) or noninvasive ventilation (NIV) followed by delayed invasive ventilation in immunocompromised patients with sepsis?

Findings: This nationwide study of over 36,000 immunocompromised sepsis patients adds to the literature indicating potential harm from prolonged NIV reliance before delayed IMV transition. We found a dose-response whereby a longer time to IMV after initial NIV was associated with stepwise mortality increases compared with upfront IMV.

Meaning: Prolonged initial NIV trials in immunocompromised patients with sepsis may be associated with increased mortality for those who ultimately require intubation.

guideline suggests conditional recommendations of NIV for immunocompromised patients with acute respiratory failure based on pooled analysis demonstrating a decrease in mortality (4). Additionally, a significant proportion of patients with NIV later progressed to require IMV. The impact of delayed transition from NIV to IMV on mortality of immunocompromised patients remains controversial (1, 5–7).

Sepsis is a life-threatening condition resulting from a dysregulated host response to infection that leads to organ dysfunction. It continues to be a major cause of morbidity and mortality worldwide, with a particularly high burden in developing countries (8, 9). As the population most susceptible to infection, immunocompromised patients faced an amplified risk of sepsis (10). Although the Surviving Sepsis Campaign guidelines provide recommendations for IMV in acute respiratory distress syndrome (ARDS) (11), but guidance on NIV is lacking. Furthermore, the current evidence predominantly focused on comparing various noninvasive ventilatory support strategies (2) and ICU patients (12). However, the majority of sepsis patients receive treatment in non-ICU settings in low- and middle-income countries (LMICs) (13, 14). This underscores the need for additional evidence regarding the benefits of transitioning from NIV to IMV for immunocompromised patients with sepsis (15, 16), particularly for patients in LMICs.

We aimed to determine whether mortality differed between initial IMV or NIV followed by delayed invasive ventilation in immunocompromised patients with sepsis. We hypothesized that prolonged reliance on failing noninvasive ventilation before intubation and IMV would negatively impact survival.

MATERIALS AND METHODS

Study Design and Data Source

This was a retrospective analysis of patient data from the National Data Center for Medical Service (NDCMS) claims database. The institutional review board of Peking Union Medical College Hospital approved the study (January 14, 2022; S-K1911; Study on the incidence and economic burden of sepsis in China) and waived the requirement for informed consent. Study procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1975. The study adhered to guidelines for accurate and transparent health estimates reporting (17).

The NDCMS database contains de-identified records for approximately half of annual hospital admissions in mainland China, as described previously (8, 18). By 2020, 3975 tertiary and secondary hospitals contributed data to NDCMS. NDCMS data undergo manual review, quality control, training, and audits to ensure accuracy. The database includes patient demographics, hospital information, admission details, diagnoses, procedures, and costs. Palliative care information was not available in the NDCMS database. Unique patient and admission identifications protect privacy while enabling record linkage. For our study, after excluding hospitals with insufficient patient identifiers (illustration in **Method S1**, http://links.lww.com/CCM/H575), 3530 hospitals remained for this analysis, capturing diverse patient populations across China. NDCMS provides insights into ventilatory support management for immunocompromised patients in China's variable-resourced hospitals. Diagnoses in the NDCMS database were coded using the official 10-digit Chinese version of the *International Classification of Diseases* (ICD), Tenth Revision diagnosis codes (an expansion from the four-digit World Health Organization version [19]) and ICD-9 procedure codes (8).

Study Population

Using the data extracted from our previous study (8), during the study period from January 1, 2017, to December 31, 2019, among patients with explicit sepsis, we enrolled the adult (age ≥ 18 y old) with immunocompromised conditions (identified using a validated ICD-9 algorithm (20), including HIV/AIDS, hematologic malignancy, solid malignancy, organ transplant, rheumatologic disease, and other immune conditions, detailed in **Table S1** (http://links.lww.com/CCM/H575) who received ventilation. Further, patients with tracheostomy (ICD-9 procedure codes of 31.1x00 or 31.2900) greater than or equal to three ventilation procedures in one episode of admission or IMV transition more than 14 days after NIV initiation were excluded (**Fig. 1**).

Exposure

The study exposure was initiation of NIV (ICD-9 procedure codes 93.90 and 93.91) or IMV (ICD-9 procedure codes 96.70, 96.71, and 96.72). Because the aim of our study was to compare initial IMV or NIV followed by delayed IMV, patients were categorized into either NIV or IMV initiation group based on the type of ventilation initiated, with the IMV initiation group serving as the reference. The date of ventilation initiation was defined as the index date.

Some patients in the NIV initiation group later require IMV. Thus, NIV patients were further categorized by time to IMV: 1) no transition, 2) immediate (≤ 1 d) transition, 3) early (2–3 d) transition, 4) delayed (4–7 d) transition, and 5) late (≥ 8 d) transition. For comparison between these further-categorized groups, IMV initiation group also served as the reference group. Additionally, to address the influence of immortal time bias (illustration in **Method S2**, http://links.lww.com/CCM/H575) when comparing five different IMV transition groups with IMV initiation group, the immortal time Some patients in the NIV initiation group later requiring IMV. Thus, NIV patients were further categorized by time to IMV: 1) no transition, 2) immediate (≤ 1 d) transition, 3) early (2–3 d) transition, 4) delayed (4–7 d) transition, and 5) late (≥ 8 d) transition. For comparison between these further-categorized groups, IMV initiation group also served as the reference group. Additionally, to address the influence of immortal time bias (illustration in Method S2, http://links.lww.com/CCM/H575) when comparing five different IMV transition groups with IMV initiation group, the immortal time Some patients in NIV initiation group later requiring IMV. Thus, NIV patients were further categorized by time to IMV: 1) no transition, 2) immediate (≤ 1 d) transition, 3) early (2–3 d) transition, 4) delayed (4–7 d) transition, and 5) late (≥ 8 d) transition. For comparison between these further-categorized groups, IMV initiation group also served as the reference group. Additionally, to address the influence of immortal time bias (illustration in Method S2, http://links.lww.com/CCM/H575) when comparing five different IMV transition groups with IMV initiation group, the immortal time—that is, time from index date to the transition to IMV—is excluded from the follow-up of patients who transited from NIV to IMV, and follow-up for these patients was started from the date when they transited to IMV (landmark date, e.g., the landmark date for patients with early transition to IMV was 2–3 d after the index date) (21).

Outcome and Covariates

The primary outcome was hospital mortality. All patients were followed from the index/landmark date to the date of discharge or death in the hospital.

Covariates extracted were age, sex, comorbidities (chronic obstructive pulmonary disease [COPD], cardiovascular disease, diabetes, etc., detailed in **Table S2**, http://links.lww.com/CCM/H575), immunocompromised conditions (HIV/AIDS, malignancies, transplant, etc.), organ dysfunctions (respiratory failure, shock, renal dysfunction, renal replacement therapy, detailed in **Table S3**, http://links.lww.com/CCM/H575), hospital-acquired sepsis, defined as the code of status at admission equals none; preoperative

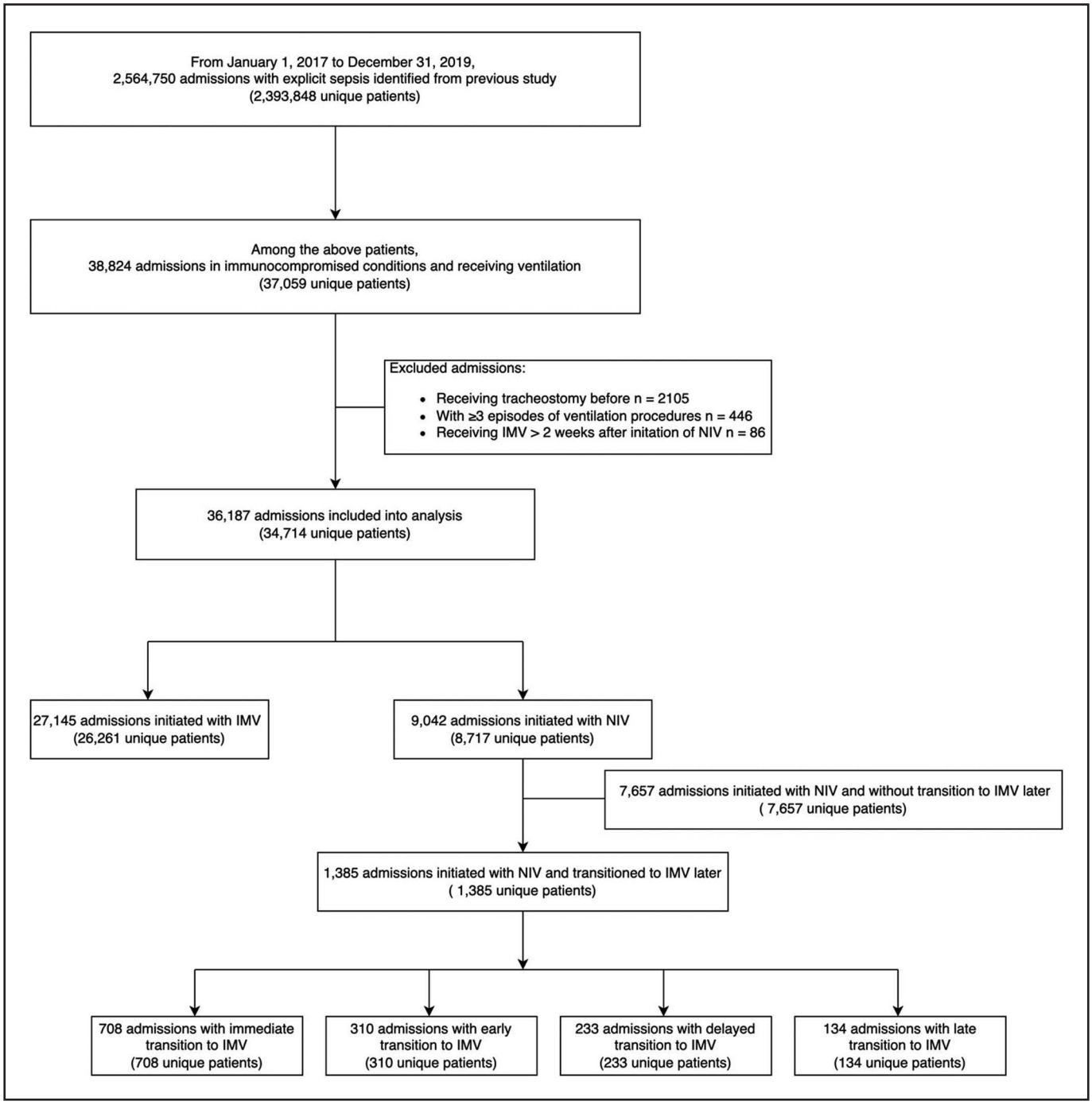

Figure 1. Flowchart of inclusion/exclusion process. Immediate transition means transition from noninvasive ventilation (NIV) to invasive mechanical ventilation (IMV) ≤ 1 d; early transition means transition from NIV to IMV within 2–3 d; delayed transition means transition from NIV to IMV within 4–7 d; late transition means transition from NIV to IMV ≥ 8 d.

sepsis, defined as sepsis occurred before or after any therapeutic or major diagnostic procedure which involves the use of instruments or the manipulation of part or parts of the body and generally takes place under Operation theater conditions, pneumonia-related sepsis (ICD-10 codes of J15.903, J18.903), and hospital-level quartiles categorized according to the number of ventilated immunocompromised patients with sepsis per year during the study period.

Statistical Analysis

Continuous variables were summarized as mean with SD or median with interquartile range (IQR),

depending on the distribution, and categorical variables were summarized as numbers and percentages.

Inverse probability of treatment weighting (IPTW) was used to adjust for confounding. We estimated the probability of NIV initiation versus IMV initiation (propensity score, PS) as a function of all study covariates mentioned previously by logistic regression model. IMV initiation patients were weighted by 1, and in the NIV initiation group by (1-PS)/PS. For the further categorization of NIV initiation group, the probabilities of no, immediate, early, delayed, and late transition to IMV versus IMV initiation were estimated by different logistic regression models, which included all study covariates, respectively. And similarly, patients in IMV initiation group were weighted by 1, and each IMV transition group was weighted by (1-PS)/PS, where PS was estimated by the corresponding logistic regression model. Standardized mean differences (SMD) were calculated to evaluate the balance of covariates between different groups before and after weighting, considering SMD greater than 0.1 as the threshold for significant imbalance.

For the primary outcome, we estimated crude hospital mortality rates per person days for all groups, and then weighted Cox regressions were conducted to estimate hazard ratios (HRs) of different kinds of IMV transition versus IMV initiation. Robust variance estimation was used to obtain 95% CIs. In addition, weighted Kaplan-Meier curves were further plotted to compare the cumulative incidences of hospital mortality of different NIV initiation groups versus NIV initiation group.

Subgroup Analysis. Subgroup analyses were performed to test for potential effect modification of age (18–65, 65–80, ≥ 80 y old), sex (male and female), and immunocompromised conditions (only solid malignancy, rheumatologic/inflammatory disease were considered here due to the limitations of sample size).

Sensitivity Analysis. Three sensitivity analyses were performed to test the robustness of our data.

First, to assess the overall impact of delayed IMV on hospital mortality, irrespective of the timing, patients were grouped together into a unified cohort (IMV all transition). Subsequently, the risk of hospital mortality for this cohort was compared with that of patients undergoing IMV initiation using IPTW. As mentioned previously, follow-up for patients in IMV transition group starts at the landmark date.

Second, even though moving the start of follow-up to the landmark date can eliminate immortal time bias, but it may introduce indication bias (indication bias occurs because the later the time patients transited to IMV, the more severe their disease conditions were) and survivor/selection bias (survivor/selection bias occurs because the longer the time between NIV initiation and transition, the higher the proportion of patients with more severe disease conditions die within that duration, leaving a greater proportion of patients with less severe disease), which will over/underestimate the effect of different IMV transitions to hospital mortality. However, the influence of which bias (indication bias vs. survivor/selection bias) is stronger remains unclear, and the direction of whether these biases would overestimate or underestimate the effects on hospital mortality is unclear. Thus, to fully solve the above problems, we used the target trial framework to make the research question explicit and to guide the design and analysis, and **Table S4** (http://links.lww.com/CCM/H575) outlines the protocol of a target trial and the emulation procedure. To compare hospital mortality risk associated with different treatment strategies (exposures in our main analysis, IMV initiation, non/immediate/early/delayed/late transition to IMV), first, through IPTW we made baseline covariates between IMV initiation and NIV initiation groups balanced, then cloning, censoring and weighting method was used for IPTW weighted patients in NIV initiation group, to further ensure the covariates balance between different kinds of IMV transition groups and IMV initiation group (detailed illustration in **Method S3**, http://links.lww.com/CCM/H575).

Last, we further excluded readmitted patients (3.4%) from our study population to assess the impact of readmitted patients on the effect of different IMV transitions versus IMV initiation on hospital mortality (one patient can only die one time, including readmitted patients may underestimate the risk of hospital mortality of all groups).

RESULTS

Baseline Characteristics

The baseline characteristics of these patients are summarized in **Table S5**, (http://links.lww.com/CCM/H575). Of 36,187 immunocompromised patients with sepsis requiring ventilation, 27,145 initiated IMV and

9,042 initiated NIV. Compared with IMV initiation patients, NIV initiation patients were older (69 ± 16 vs. 66 ± 15 y old) with more COPD (21% vs. 14%), respiratory failure (64% vs. 48%), and pneumonia sepsis (92% vs. 81%). In contrast, NIV initiation patients had lower rates of malignancy (30% vs. 38%), septic shock (23% vs. 42%), renal dysfunction (21% vs. 33%), renal replacement therapy (7% vs. 15%), hospital-acquired (12% vs. 21%), and perioperative (5% vs. 20%) sepsis. More patients received NIV than IMV (31.2% vs. 22.4%) in hospitals with the highest case volume of ventilated immunocompromised sepsis. After weighting, baseline characteristics were balanced between the groups (**Table S6**, http://links.lww.com/CCM/H575). Of 9,042 NIV patients, 15.3% later transitioned to IMV (median 1 [IQR 1–4] d; **Fig. S1**, http://links.lww.com/CCM/H575). The immediate transition group had 708 patients, early 310 patients, delayed 233 patients, and late 134 patients. The proportion of septic shock was higher in the immediate transition group than other four groups with NIV. Although more patients in early/delayed/late transition had renal dysfunction and hospital-acquired sepsis than nontransition/immediate transition group. After weighting, all covariates between each IMV transition group and IMV initiation group were well balanced (**Fig. S2**, http://links.lww.com/CCM/H575).

Comparison of NIV Initiation With No/Immediate/Early/Delayed/Late IMV Transition Versus IMV Initiation

Over a median follow-up of 9 days (IQR 3–18), NIV initiation had a similar adjusted mortality compared with IMV initiation (HR 1.006; 95% CI, 0.959–1.012) (**Table 1**; and **Fig. S3**, http://links.lww.com/CCM/H575). However, when patients initiated on NIV were further categorized by time to transition, a dose-response relationship emerged between longer time to transition and higher mortality risk relative to IMV initiation. Specifically, the NIV nontransition group had lower mortality than IMV initiation (HR 0.942, 95% CI, 0.893–0.993). In contrast, mortality risk increased progressively from immediate transition (HR 1.650; 95% CI, 1.470–1.852) to late transition (HR 2.507; 95% CI, 1.969–3.192). The cumulative incidence curves visually demonstrated this dose-response relationship, with early separation from IMV initiation that widened over follow-up. For example, 10-day mortality

TABLE 1.
Number of Events, Incidence Rates, and Crude and Adjusted Hazard Ratios for the Association Between Noninvasive Ventilation Initiation (With Different Kinds of Transition to Invasive Mechanical Ventilation) Versus Invasive Mechanical Ventilation Initiation and Hospital Mortality

Groups	No. of Patients	Follow-Up (Median [Interquartile Range])	No. of Events	Person-Days	Incidence Rate/ Person-Days (95% CI)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Invasive mechanical ventilation initiation	27,145	8 (3–17)	9,677	356,894	0.0271 (0.0266–0.0277)	1 (reference)	1 (reference)
Noninvasive ventilation initiation	9,042	10 (4–18)	3191	119,848	0.0266 (0.0257–0.0276)	0.928 (0.891–0.966)	1.006 (0.959–1.055)
No transition	7,657	10 (4–18)	2534	103,225	0.0246 (0.0236–0.0255)	0.861 (0.824–0.9)	0.942 (0.893–0.993)
Immediate transition	708	5 (2–12)	316	6,511	0.0485 (0.0435–0.0540)	1.66 (1.484–1.857)	1.65 (1.47–1.852)
Early transition	310	5 (3–12)	153	2,764	0.0554 (0.0473–0.0645)	1.802 (1.536–2.114)	1.806 (1.548–2.109)
Delayed transition	233	4 (2–10)	111	1,890	0.0588 (0.0488–0.0702)	2.116 (1.755–2.551)	2.089 (1.719–2.54)
Late transition	134	4 (2–9)	77	1,351	0.0756 (0.0704–0.0810)	2.514 (2.009–3.146)	2.507 (1.969–3.192)

HR = hazard ratio.
[a]Adjusted for all covariates, including age, sex, comorbidities, immunocompromised conditions, sources of sepsis, and hospital-level quartiles by inverse probability of treatment weighting. Immediate transition means transition from noninvasive ventilation (NIV) to invasive mechanical ventilation (IMV) ≤ 1 d; Early transition means transition from NIV to IMV within 2–3 d; delayed transition means transition from NIV to IMV within 4–7 d; Late transition means transition from NIV to IMV ≥ 8 d.

was 58.52% (95% CI, 55.9–61.14%) for late transition, 51.83% (95% CI, 49.71–53.95%) for delayed transition, 46.61% (95% CI, 44.89–48.34%) for early transition, 44.06% (95% CI, 42.86–45.25%) for immediate transition, 27.72% (95% CI, 27.14–28.29%) for no transition, 29.08% (95% CI, 28.52–29.63%) for IMV initiation (**Fig. 2**).

Subgroup and Sensitivity Analyses

The dose-response relationship between longer transition time and higher mortality was also observed across subgroups of age, sex, and immunocompromised conditions (**Table 2**).

In a sensitivity analysis combining all IMV transition groups, mortality remained higher when compared with IMV initiation (HR 1.721; 95% CI, 1.588–1.866) (**Table S7**, http://links.lww.com/CCM/H575). Using a target trial framework to emulate randomization found similar results but with less smoothly increasing mortality risk associated with longer transition time (**Table S8**, http://links.lww.com/CCM/H575). Excluding readmitted patients and patients who initiated NIV or IMV in the ICU also did not meaningfully change the mortality hazards for delayed IMV transition (**Tables S9** and **S10**, http://links.lww.com/CCM/H575).

DISCUSSION

In this retrospective study of over 36,000 immunocompromised patients with sepsis requiring mechanical ventilation, we found that prolonged reliance on NIV before transitioning to IMV was associated with higher in-hospital mortality compared with initial IMV. The risk of death showed a dose-response relationship, with mortality HRs increasing from 1.65 for immediate transition to 2.51 for late transition at least 8 days after NIV initiation. These findings were robust across subgroups and in sensitivity analyses. To our knowledge, this study was the first nationwide comparison of the benefit of NIV and IMV for immunocompromised patients with sepsis in LMICs.

Our findings align with prior research, highlighting the potential adverse effects of delayed intubation subsequent to the initial application of NIV in broad populations with ARDS. In a single-center investigation involving 175 patients, Kang et al (16) identified a two-fold rise in the likelihood of hospital mortality when intubation was postponed beyond 48 h following unsuccessful high-flow nasal cannula utilization. In their analysis of 457 patients with ARDS, Kangelaris et al (5) reported an adjusted HR of 2.37 for mortality in the late intubation group, contrasting

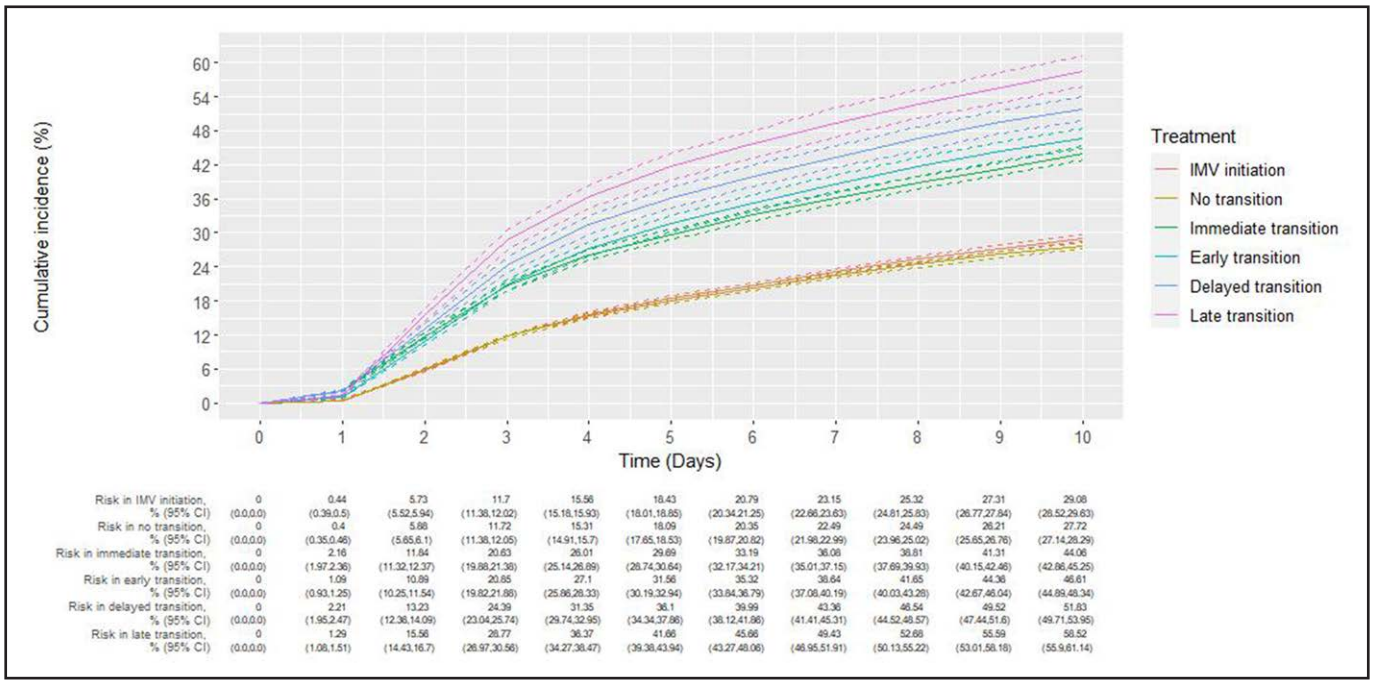

Figure 2. Weighted cumulative incidence curve of hospital mortality for different invasive mechanical ventilation (IMV) transitions vs. IMV initiation. Immediate transition means transition from noninvasive ventilation (NIV) to IMV less than or equal to 1 d; early transition means transition from NIV to IMV within 2–3 d; delayed transition means transition from NIV to IMV within 4–7 d; late transition means transition from NIV to IMV ≥ 8 d.

TABLE 2.

Subgroup Analysis of Adjusted Hazard Ratios for the Association Between Noninvasive Ventilation Initiation (With Different Kinds of Transition to Invasive Mechanical Ventilation) Versus Invasive Mechanical Ventilation Initiation and Hospital Mortality

Subgroups	No. of Patients	Invasive Mechanical Ventilation Initiation, HR	Noninvasive Ventilation Initiation, HR (95% CI)				
			No Transition	Immediate Transition	Early Transition	Delayed Transition	Late Transition
Age category							
18–65 y old	14,037	1 (reference)	0.74 (0.67–0.82)	1.45 (1.2–1.75)	1.54 (1.17–2.01)	1.65 (1.12–2.44)	2.64 (1.78–3.91)
65–80 y old	14,101	1 (reference)	0.92 (0.84–1.01)	1.83 (1.51–2.21)	1.94 (1.54–2.45)	2.6 (1.94–3.5)	2.79 (1.94–4.01)
≥80 y old	8,049	1 (reference)	1.27 (1.17–1.38)	1.81 (1.45–2.26)	2.06 (1.48–2.86)	1.87 (1.32–2.66)	1.91 (1.13–3.23)
Sex							
Male	24,856	1 (reference)	0.96 (0.9–1.03)	1.66 (1.44–1.91)	1.74 (1.44–2.11)	2.09 (1.66–2.62)	2.81 (2.13–3.71)
Female	11,331	1 (reference)	0.9 (0.82–0.98)	1.64 (1.34–2.01)	1.92 (1.48–2.49)	2.11 (1.43–3.11)	1.96 (1.22–3.14)
Immunocompromised conditions							
Solid malignancy	13,028	1 (reference)	1.11 (1.02–1.2)	1.9 (1.54–2.36)	2.11 (1.63–2.72)	2.59 (1.76–3.82)	3.21 (2.17–4.75)
Rheumatologic/ inflammatory disease	16,520	1 (reference)	0.89 (0.82–0.96)	1.8 (1.53–2.11)	1.71 (1.35–2.16)	2.32 (1.79–3)	3 (2.21–4.08)

HR = hazard ratio.

Immediate transition means transition from noninvasive ventilation (NIV) to invasive mechanical ventilation (IMV) ≤1 d; early transition means transition from NIV to IMV within 2–3 d; delayed transition means transition from NIV to IMV within 4–7 d; late transition means transition from NIV to IMV ≥ 8 d.

it with the cohort of patients intubated on the onset day of ARDS. Our results align with the latest meta-analysis from a comprehensive, collaborative network (12), which indicates a substantial rise in the risk of death associated with delayed intubation for immunocompromised patients ultimately requiring IMV due to respiratory failure. Although immunocompromised patients inherently encounter heightened mortality risks with invasive ventilation (3), our findings add to the expanding evidence indicating that an extended trial of NIV may result in adverse outcomes if it leads to delays in essential intubation.

Some potential reasons for this association warrant discussion. Prolonged NIV may increase the risk of ventilator-induced lung injury by exerting repeated opening and collapsing of unstable lung units (22). With NIV, some patients might generate substantial intrathoracic pressure swings and tidal volumes, potentially leading to excessive work of breathing, increased oxygen consumption, or cardiac overload (3). NIV intolerance can lead to exhaustion and agitation that precipitate emergency reintubation in a more unstable condition (3). Prolonged NIV may also increase the risk of pneumonia (23). Additionally, clinical inertia or a default strategy of trying NIV first may delay needed intubation (24).

An interesting finding in our study was that a majority (84.7%) of immunocompromised patients initiated with NIV never required IMV, and these patients had a better outcome than patients on IMV as shown in Table 1. This finding was consistent with existing data showing NIV is an option in immunocompromised patients (4). Meanwhile, the observed increased mortality risk with delayed IMV group highlights the need for frequent NIV assessments and shorter trials in sepsis populations. Easily measured parameters like heart rate, acidosis, consciousness, oxygenation, and respiratory rate should be evaluated to guide transition decision-making (25, 26). We also found that 75% of immunosuppressive septic patients received IMV (27,145) without NIV (9,042). This finding was consistent with a recent study in China, indicating that 79.1% of sepsis patients in ICUs received IMV (27). Although there is no comprehensive nationwide guideline for initiating NIV or direct intubation in immunosuppressed septic patients, our extensive cohort offers insights into real-world practices and outcomes across various Chinese hospitals. These findings emphasize the urgent need for further investigations.

This study has limitations. First of all, given its observational nature, the analysis remains susceptible to unmeasured confounding and a variety of biases despite using extensive adjustment techniques. For example, our database lacks physiologic parameters to define indications of ventilation and NIV failure, as well as data on the reasons for intubation in the delayed IMV group, ICU stays, cause of mortality and palliative care for outcome measurements. Consequently, the complete elimination of confounding influences is unattainable, highlighting the importance of cautious interpretation of the results. Nevertheless, our extensive cohort offers insights into real-world practices and outcomes across various Chinese hospitals, underscoring the critical need for additional research in this area. Second, although our statistical methods addressed immortal time and indication bias, the possibility of residual confounding persists. Third, the generalizability of our results to different health systems with diverse intensive care capacities or NIV protocols may be limited. Fourth, our study was an ICD-based study. An explicit coding algorithm inevitably underestimated patients with respiratory failure (8, 28). This limitation explains why only 64% of the NIV group and 48% of the IMV group were identified as having respiratory failure. Conversely, an implicit coding algorithm that includes ventilation-related procedures would result in identifying 100% of patients as having respiratory failure, which was not applicable in this study.

CONCLUSIONS

This nationwide study suggests immunocompromised patients with sepsis would benefit from tolerated NIV not requiring intubation, and prolonged initial NIV trial may be associated with higher mortality in patients ultimately requiring intubation. Frequent NIV monitoring and intubation preparedness are warranted in this high-risk population.

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China Critical Care Clinical Trials Group (CCCCTG) members are listed in a ***Supplementary Appendix 1*** *(http://links.lww.com/CCM/H587). China National Critical Care Quality Control Center Group members are listed in* ***Supplementary Appendix 2*** *(http://links.lww.com/CCM/H588).*

Drs. Weng, Xu, and Du designed the study and invited researchers to participate in the study. Xu and Liu performed statistical analysis. Drs. Weng, Xu, Y.F. Wang, Dong, Chen, Y. Wang, and Du wrote and edited the article.

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