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Research Article

Clinical Characteristics and Survival Outcomes of Invasive Mechanically Ventilated COVID-19 Patients: A Single-Center Study from Iran

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ABSTRACT

Background: COVID-19 patients requiring invasive mechanical ventilation represent the most severe cases with high mortality rates. This study aimed to analyze survival outcomes and identify prognostic factors in a cohort of invasive mechanically ventilated COVID-19 patients in Iran.
Methods: In this retrospective cohort study, we analyzed 639 adult COVID-19 patients who underwent invasive mechanical ventilation at Al-Zahra Hospital's ICUs in Isfahan. Survival analysis and Cox regression models were used to identify factors associated with mortality.
Results: Among 639 mechanically ventilated patients, mortality was 87.9%. The mean age was 63.01±16.4 years. 59.8% of participants were male. Hypertension (42.6%), diabetes (33.8%), and cardiovascular disease (25.0%) were the most prevalent comorbidities. The overall median survival time was 35 days. Cox regression analysis identified significant mortality predictors, including male sex (HR=3.489, 95% CI: 1.150-10.585), age (HR=1.064, 95% CI: 1.024-1.106), cardiovascular disease (HR=1.445, 95% CI: 1.096-1.905), higher APACHE IV score (HR=1.028, 95% CI: 1.005-1.051), and delayed mechanical ventilation after disease onset (HR=1.111, 95% CI: 1.031-1.196).
Conclusion: COVID-19 patients with invasive mechanical ventilation demonstrated high mortality rates. Older age, male sex, cardiovascular disease, higher APACHE IV score, and delayed mechanical ventilation after symptom onset were significant predictors of mortality. These findings highlight the importance of timely intervention in high-risk patients and may help optimize resource allocation during future pandemic waves.

Introduction

The Coronavirus Disease 2019 (COVID-19) is a serious illness caused by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has caused a significant burden on health-care systems. The World Health Organization declared COVID-19 a public health emergency of international concern in January 2020 and a pandemic in March 2020 [1-4]. COVID-19 may manifest as a mild respiratory

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infection or severe pneumonia. Elevated pro-inflammatory cytokines and unregulated immune response were identified as major predictors of severity. Severe cases of tachypnea, hypoxia, and dyspnea may progress to acute respiratory distress syndrome (ARDS), often requiring intensive care. Patients with critically low oxygen levels (SpO2 below 90%) despite supplemental oxygen or severe dyspnea unresponsive to non-invasive support may need endotracheal intubation and mechanical ventilation. For COVID-19 patients, mechanical ventilation may be necessary if they show persistent hypoxemia (PaO2/FiO2 ratio under 150 mmHg), rapid breathing, deteriorating mental status, or unstable hemodynamics [3,5-8]. Several factors, such as age, gender, ethnicity, and underlying diseases such as hypertension, diabetes, cardiovascular disease, and chronic obstructive pulmonary disease, have been found to be associated with COVID-19 severity and mortality. In addition, laboratory indicators, proinflammatory cytokine levels, and complications all showed a substantial impact on disease outcomes [3,9-12]. In Iran, during the pandemic, hospitals and ICUs experienced multiple waves of patients with varying mortality rates, respiratory failure management approaches, and patient characteristics. This study aims to analyze survival outcomes in a national cohort of adult COVID-19 patients admitted to Al-Zahra Hospital's ICUs in Isfahan and determine how patient characteristics and mechanical ventilation strategies were associated with mortality.

Methods

This retrospective cohort study investigated patients with COVID-19 who were admitted to ICUs of Al-Zahra Hospital and underwent invasive mechanical ventilation from March 2020 to September 2021. The study was approved by the Research Committee of Isfahan University of Medical Sciences and was confirmed by the Ethics Committee (Ethics Approval ID: IR.MUI.MED.REC.1402.204).

Inclusion criteria were: 1. Patients aged 18 years or older 2. Patients with a positive PCR test for COVID-19 3. Admitted in ICU 4. Underwent invasive mechanical ventilation. The exclusion criteria were: 1. Patients whose chief complaint for hospital or ICU admission was not COVID-19 infection, and they became infected during hospitalization. 2. Cases who experienced cardiac arrest within the first 24 hours of hospitalization 3. Patients with incomplete medical records.

The medical records of eligible patients were reviewed by two medical students, and demographic information, history of previous illnesses, duration of invasive mechanical ventilation, the timing of ventilation initiation after disease onset and ICU admission, Acute Physiologic Assessment and Chronic Health Evaluation 4 (APACHE IV score) at ICU admission, and patient outcomes (death/survival) were collected. Quantitative variables were reported as mean and standard deviation (mean ± SD), and qualitative variables were presented as numbers and percentages (n, %). To compare the means of parametric continuous variables, independent t-tests were utilized. The chi-squared test was used for categorical variables. The Cox regression was utilized to assess factors influencing the time to death. A p-level < 0.05 is considered statistically significant. Data were analyzed using SPSS version 26.

Results

During the study period spanning from March 2020 to September 2021, Al-Zahra Hospital's ICUs initially admitted 1,500 COVID-19 patients. After carefully applying inclusion and exclusion criteria, only 639 cases were included in our study, and the remaining cases were excluded due to not meeting invasive mechanical ventilation indications, patients aged less than 18 years, cases with non-COVID-19 chief complaints, and cases with incomplete medical records.

The study demonstrated a significant mortality rate, with 562 patients (87.9%) dying and 77 patients (12.1%) surviving. The mean age of the study population was 63.01 ± 6.4 years. Of these, 382 patients (59.8%) were male, and 257 patients (40.2%) were female. Among comorbidities, hypertension was most common, affecting 272 patients (42.6%). Diabetes came next, found in 216 patients (33.8%). Cardiovascular disease and chronic kidney disease affected 160 patients (25.0%) and 70 patients (11.0%), respectively. The baseline characteristics of the study cases are presented in (Table 1).

The survival time analysis revealed an overall median survival time of 35.0 days (95% CI: 31.59-38.41) and a mean survival time of 40.83 days (95% CI: 34.96-46.69) (Figure 1). After stratification by hypertension status, patients without hypertension had a median survival time of 36.0 days (95% CI: 30.94-41.06) and a mean survival time of 39.22 days. In comparison, patients with hypertension had a median survival time of 35.0 days (95% CI: 26.58-43.42) and a mean survival time of 38.77 days (95% CI: 32.21-45.34). No difference in survival time was detected by the log-rank test between hypertension patients and non-hypertension patients (χ^2 = 0.016, p = 0.899). In terms of diabetes status, the non-diabetic patients had a median survival time of 36.0 days (95% CI: 29.96-42.04) and a mean survival time of 40.65 days (95% CI: 33.55-47.75). Diabetic patients had a lower median survival time of 30.0 days (95% CI: 25.03-34.98) as well as a mean survival time of 36.97 days (95% CI: 29.12-44.82). However, the log-rank test revealed no statistically significant difference in survival distributions among the diabetes groups (χ^2 = 0.742, p = 0.389).

T-test analysis demonstrated significant differences in the distribution of age (p = .000, 95% CI [5.092, 12.497]), cardiovascular disease (p = 0.046, 95% CI [1.096, 1.905]), the timing of invasive mechanical ventilation after disease onset (p = .009, 95% CI [0.639, 3.124]), and the timing of invasive mechanical ventilation after ICU admission (p = .003, (95% CI [0.639, 3.124]) between the dead and survived patients. However, other variables, such as mechanical ventilation duration, oxygen saturation upon intubation, APACHE IV score, diabetes, hypertension, and chronic kidney disease histories, had no statistically significant differences between the groups (Table 1).

The Cox proportional hazards model provided more detailed insights into 28-day survival following invasive mechanical ventilation. Several variables, such as male sex, age, cardiovascular disease, mechanical ventilation duration, interval between disease onset and ventilation initiation, and APACHE IV score, were indicated as statistically significant predictors for survival (Table 2).

Table 1- Demographic, clinical characteristics, and medical history of mechanically ventilated COVID-19 patients.

Variable	Total	Alive	Dead	P value
Number	639	77(12.1%)	562(87.9%)	
Age	63.01 ± 6.4	55.29±16.40	64.08±15.28	0.000
Sex				0.080
Female	257(40.21%)	39(51.3%)	218(38.8%)	
Male	382(59.78%)	37(48.7%)	345(61.3%)	
Hypertension	272(42.56%)	31(40.25%)	241(42.88%)	0.649
Diabetes	216(33.80%)	28(36.8%)	188(33.5%)	0.643
Cardiovascular disease	160(25.03%)	11(14.5%)	149(26.5%)	0.046
Chronic kidney disease	70(10.95%)	3(3.9%)	67(11.9%)	0.577
Mechanical ventilation duration	9.51±9.77	9.25±7.48	9.55±10.02	0.818
Timing of mechanical ventilation after ICU admission	2.88±4.78	1.19±2.19	3.07±4.96	0.000
Timing of mechanical ventilation after disease onset	7.24±8.74	4.49±5.09	7.56±9.02	0.000
Oxygen saturation at intubation	72.09 ±13.76	70.47±17.17	72.25±13.38	0.471
APACHE IV score	34.46±19.12	35.51±21.93	34.37±18.76	0.661

APACHE IV score; Acute Physiologic Assessment and Chronic Health Evaluation IV score.

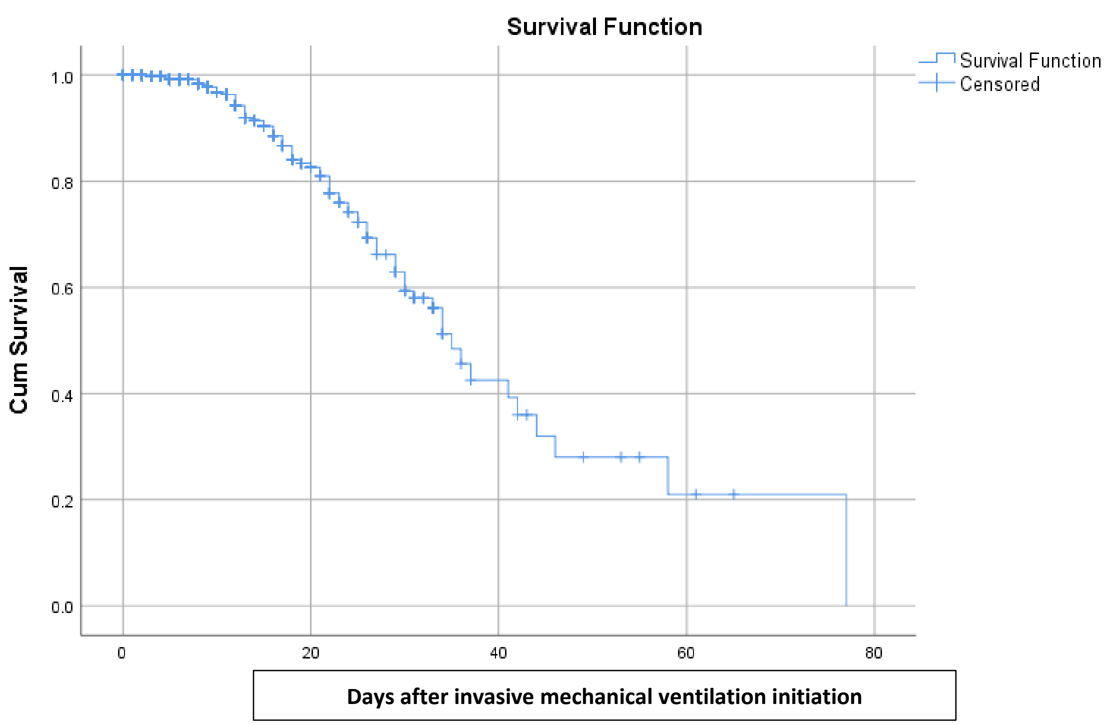

Figure 1- A: Kaplan-Meier survival curve showing cumulative survival probability over time following invasive mechanical ventilation initiation.

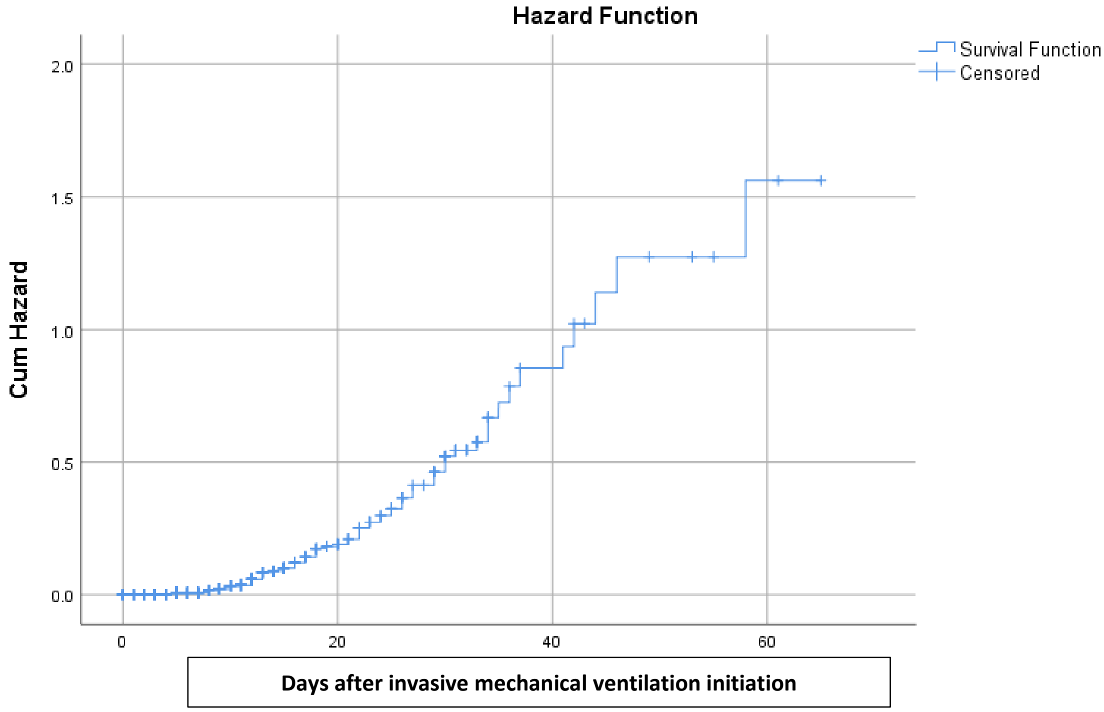

Figure 1- B: Cumulative hazard function following invasive mechanical ventilation initiation.

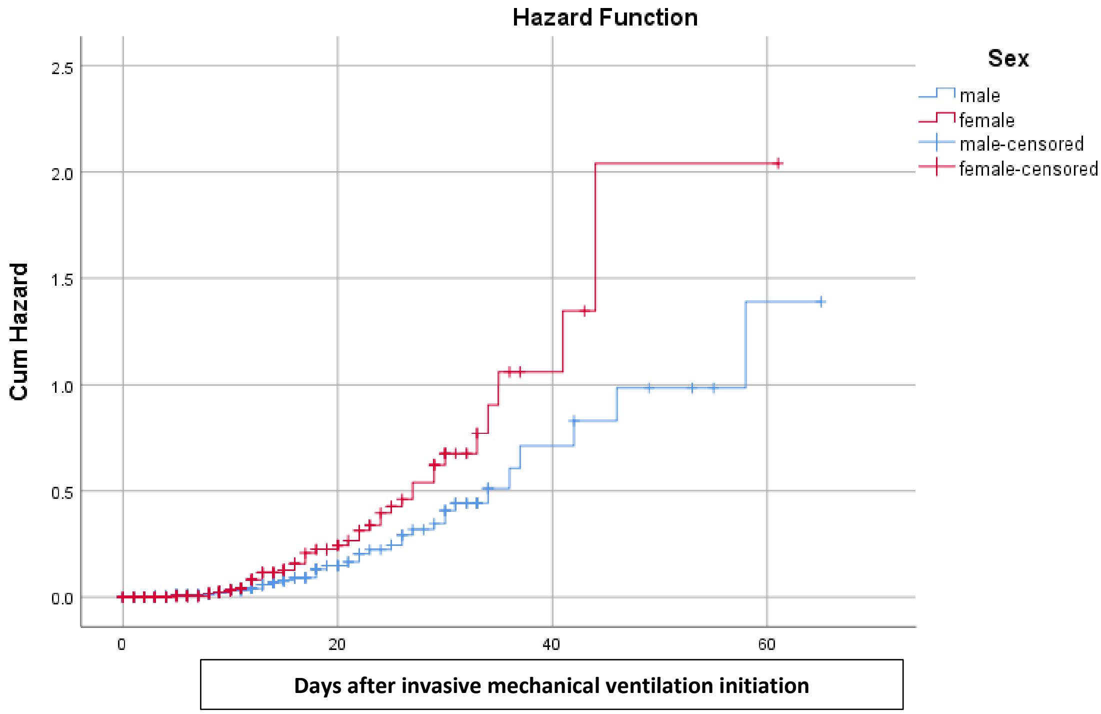

Figure 1- C: Cumulative hazard functions comparing mortality risk between male and female patients following invasive mechanical ventilation initiation.

Table 2- Factors associated with mortality in invasive mechanically ventilated COVID-19 patients.

Variable	Hazard ratio	P value	CI 95 %
Sex	3.489	0.027	(1.150-10.585)
Age	1.064	0.001	(1.106- 1.024)
Hypertension	0.350	0.177	(0.076-1.605)
Diabetes	2.553	0.220	(0.571-11.412)
Cardiovascular disease	1.445	0.009	(1.096-1.905)
Chronic kidney disease	1.220	0.865	(0.123-12.070)
Mechanical ventilation duration	0.751	0.000	(0.676-0.835)
Timing of mechanical ventilation after ICU admission	1.124	0.234	(0.926-1.364)
Timing of mechanical ventilation after disease onset	1.111	0.005	(1.031-1.196)
Oxygen saturation at intubation	1.012	0.511	(0.976-1.051)
APACHE IV score	1.028	0.017	(1.005-1.051)

APACHE IV score; Acute Physiologic Assessment and Chronic Health Evaluation IV score.

Discussion

In this study conducted on 639 cases of COVID-19 who were admitted to the ICU and underwent invasive mechanical ventilation, the mortality rate was 87.9%, and the overall mean survival time was approximately 41 days. Older age, male sex, cardiovascular disease history, invasive mechanical ventilation duration, APACHE IV score, and the timing of invasive mechanical ventilation after disease onset were associated with mortality. A mortality rate of 87.9% was observed in our study. This is consistent with a number of other reports that have described the mortality rate among patients with COVID-19 who received invasive mechanical ventilation, which ranged from 81% [13], 82% [14], 84% [15], 86% [16-17], and 88% [18]. However, the observed mortality rate in our study exceeds some other reports. In 2021, a meta-analysis by Li et al. on patients with COVID-19 requiring invasive mechanical ventilation included 69 studies, and the overall case fatality rate was 45%; however, the range of case fatality rates among all studies was 0-100% [19]. In another review, 2021 ICU admission mortality following intubation was found to be 15 to 36% [3]. This discrepancy may be attributed to several factors, including healthcare system capacity during peak pandemic periods, the severity of cases admitted to our study, differences in patient demographics, variations in treatment and management, and also differences in viral variants.

Our survival analysis demonstrated an overall median survival time of 35.0 days (95% CI: 31.59-38.41) and an overall mean survival time of 41 days for the entire cohort. The Cox proportional hazards model identified several significant predictors of 28-day survival following mechanical ventilation. Sex showed a hazard ratio of 3.489 (95% CI: 1.150-10.585), indicating that male patients had a substantially higher risk of mortality, which aligns with previous studies [20-24]. This finding might be attributed to factors like differences in baseline immune systems and differences in immune responses between the two genders [25].

Our analysis demonstrated that age was a significant predictor of mortality in our population (p=.000, 95% CI [5.092, 12.497]). The Cox proportional hazards model further confirmed age as an independent risk factor with a hazard ratio of 1.064 (95% CI: 1.024-1.106), indicating that each additional year of age increased mortality risk by 6.4%. These findings align with a vast amount of previous studies, indicating that older age is an important predictor of poor outcomes in COVID-19 cases [26-32]. Similarly, in a case-cohort study conducted in Iran, age had HR= 1.06, $p < 0.001$, indicating each one-year increase in age increased the risk of mortality by 6% [31]. Moreover, in another study in Iran, on 17,286 patients, they reported cases over 60 years of age have a significantly increased risk of in-hospital mortality, approximately 2 times higher than that in younger individuals [26]. A meta-analysis by Romero Starke et al. found an 8% rise in the risk of death per year of age (95% CI 3–13%) [32]. This finding can be attributed to several factors, such as the age-related decline in immune function, higher comorbidity in the elderly, and atypical presentation of COVID-19 in old patients resulting in delayed diagnosis and treatment [33-35].

In our research, consistent with earlier studies, hypertension, diabetes, and cardiovascular disease were prevalent comorbidities among COVID-19 patients who were admitted to the ICU [36-38]. Cardiovascular disease emerged as an important predictor of mortality (p=0.046) and, furthermore, as a prognostic factor with a hazard ratio of 1.445 (95% CI: 1.096-1.905), confirming its role as a significant predictor of poor outcomes. Similarly, a systematic review reported that cardiovascular disease was significantly correlated with mortality in COVID-19 cases [39]. Moreover, in a study by Gholinataj et al. on 391 patients with COVID-19 admitted to the ICU, cardiovascular disease was correlated to increased mortality. In another study of 187 COVID-19 patients who were admitted to the subintensive and ICUs, cardiovascular disease, except for coronary artery disease, was associated with mortality [9]. The pathophysiologic mechanisms between COVID-19 and cardiovascular disease include the interaction between SARS-CoV-2 and the Angiotensin-Converting Enzyme 2 (ACE2) receptor, which is incredibly found in heart tissues. This interaction can lead to endothelial dysfunction and worsen pre-existing cardiac disease. The ACE2 receptor is used as a gateway by the virus to enable it to reach cells by interacting with its spike protein. Consequently, patients with cardiovascular diseases are believed to be at a higher risk for severe COVID-19 [40-41].

While hypertension (42.6%), diabetes (33.8%), and chronic kidney disease (11.0%) were common comorbidities in our population, they did not show significant differences between dead and survivor groups, and additionally, survival analysis did not find statistically significant differences in survival time between patients with and without these conditions. These findings contrast with some earlier studies that identified hypertension and diabetes as important risk factors for mortality in COVID-19 individuals [42-45]. However, our findings align with a cohort study conducted by Rosentha et al. suggesting that after adjusting for age and other confounders, hypertension may not be significantly associated with in-hospital mortality (aOR=1.08; 95% CI, 0.99-1.18; P = .07) [46].

The APACHE IV score demonstrated a significant association with mortality (HR= 1.028, 95% CI: 1.005-1.051), confirming its utility as a prognostic factor in COVID-19 patients requiring invasive mechanical ventilation. In a cohort study in China in 2020, the Acute Physiology and Chronic Health Evaluation II score (APACHE II score) was found as a valuable tool for predicting hospital mortality in patients with COVID-19 [47]. In another study by Vandenbrande et al., the APACHE IV score demonstrated a very good ability to predict mortality in very ill COVID-19 cases, even better than the APACHE 2 score [48]. The significant effect of the APACHE IV score in our study emphasizes the importance of baseline disease severity in determining patient outcomes, and it can be incorporated into clinical decision-making and may help optimize resource allocation in resource-constrained settings during pandemics. Regarding the timing of invasive mechanical ventilation after disease onset, it was significantly associated with mortality, with the dead group showing longer time intervals between disease onset and invasive mechanical ventilation compared to survivors (p=.000). The Cox regression analysis confirmed this association with a hazard ratio of 1.111 (95% CI: 1.031-1.196), indicating that each additional day of delay in invasive mechanical ventilation after symptom onset increased mortality risk by 11.1%. There are ongoing debates regarding the optimal timing of intubation in COVID-19 patients. Early in the pandemic, there was a tendency toward early intubation based on concerns about patient self-inflicted lung injury (P-SILI) and rapid deterioration [49-50]. The pathophysiological explanation for this finding is that prolonged exposure to the high respiratory effort before intubation may exacerbate lung injury through increased transpulmonary pressures and tidal volumes, leading to patient self-inflicted lung injury [51]. However, as the pandemic progressed, some centers and studies revealed that more conservative approaches, such as utilizing high-flow nasal oxygen and non-invasive ventilation, are associated with a lower risk of intubation and death to potentially avoid intubation [52]. Our findings imply that delayed intubation may be deleterious, possibly due to progressive lung injury from prolonged respiratory distress. This aligns with findings from Vera et al., who reported that delayed intubation in COVID-19 patients was associated with higher ICU mortality [53]. Similarly, a multicenter study by Zhang et al. found that delaying intubation in patients who eventually require invasive mechanical ventilation may lead to higher mortality [54]. In contrast to the previous studies and our findings, several investigations revealed no significant association between early and late intubation and the risk of mortality [55-56]. It's important to acknowledge that the relationship between invasive mechanical intubation timing and outcomes is complex and may be confounded by the patient’s illness severity and resource availability [57].

Conclusion

This study revealed a high mortality rate of 87.9% in COVID-19 cases admitted to ICUs. Advanced age, male sex, cardiovascular disease, higher APACHE IV score at ICU admission, and delayed initiation of mechanical ventilation after symptom onset were found to be associated with mortality. The association between delayed intubation and increased mortality suggests the importance of timely intervention in deteriorating patients. Our findings contribute to understanding prognostic factors in critically ill COVID-19 patients and may help inform clinical decision-making during future pandemic waves.

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