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The impact of dexamethasone on short- and long-term mortality in hospitalized COVID-19 patients: a retrospective study

Jian Zhao[1†], Hui Hua Jiang[1†], Hong Hong Wan[1†], Dan Liu[1†], Yi Zhao[1†], Yan Qing Chen[1*] and Yuan Zhuo Chen[1*]

Abstract

Background Dexamethasone has been widely used in treating severe COVID-19 patients due to its anti-inflammatory properties. However, its long-term impact on mortality remain unclear.

Objective To evaluate the effect of dexamethasone on short-term (28-day) and long-term (1-year) mortality in hospitalized COVID-19 patients and to explore its efficacy across different respiratory support.

Methods A retrospective cohort study was conducted using the MIMIC-IV (v3.0) database. A total of 576 confirmed COVID-19 patients were included, with 288 patients receiving dexamethasone and 288 not receiving it, matched by propensity scores. Survival analyses assessed the impact of dexamethasone on mortality, and subgroup analyses were performed based on the type of respiratory support received.

Results After propensity score matching, dexamethasone treatment was associated with reduced mortality at both 28 days (adjusted HR 0.67, 95% CI 0.46–0.99, $P=0.045$) and 1 year (adjusted HR 0.66, 95% CI 0.47–0.92, $P=0.014$). Subgroup analysis revealed differential treatment effects by respiratory support type (P for interaction = 0.001 at 28 days and 0.004 at 1 year). The survival benefit was most pronounced in patients receiving NIV (28-day adjusted HR 0.15, 95% CI 0.05–0.42, $P<0.001$) and significant in those receiving IMV (28-day adjusted HR 0.62, 95% CI 0.39–0.99, $P=0.045$), while no significant benefit was observed in patients receiving oxygen therapy alone.

Conclusion This retrospective study suggests that dexamethasone treatment was associated with reduced mortality in hospitalized COVID-19 patients, particularly in those receiving NIV or IMV. These findings add to the evidence supporting dexamethasone use in severe COVID-19 patients requiring respiratory support.

Keywords Dexamethasone, COVID-19, Mortality, MIMIC-IV, Retrospective study, Respiratory support

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Introduction

COVID-19, caused by the SARS-CoV-2 virus, has led to millions of infections and severe respiratory complications worldwide since the outbreak in 2020. According to the latest data from the World Health Organization, as of September 2024, there have been more than 700 million confirmed cases globally, with over 6.9 million deaths [1, 2]. Despite significant advances in vaccination and treatment methods that have substantially reduced mortality rates, COVID-19 continues to pose a cyclical threat to public health in several regions. This is particularly evident in critically ill patients requiring hospitalization and respiratory support, where mortality remains significantly higher than in the general population.

In COVID-19 patients, an excessive inflammatory response is a major driver of respiratory failure, organ dysfunction, and death. Dexamethasone, by suppressing the immune system's hyperactive response, has been shown to significantly reduce mortality, especially in critically ill patients [3]. Recognized as a cornerstone of COVID-19 treatment, dexamethasone's efficacy has been widely acknowledged, particularly in patients requiring respiratory support [4]. The RECOVERY trial was the first large-scale study to demonstrate the substantial impact of dexamethasone in reducing mortality among critically ill COVID-19 patients, particularly those on mechanical ventilation [5]. Since then, numerous studies have supported these findings, showing that dexamethasone plays a critical role in mitigating the severe inflammatory response triggered by COVID-19 [6, 7].

However, despite widespread recognition of its efficacy in critically ill patients, the long-term effects of dexamethasone remain unclear. The optimal dose, timing of administration, and duration of treatment continue to be topics of active investigation [8, 9]. Many existing studies focus on short-term outcomes, such as 28-day mortality, but systematic research on its long-term effects, such as 1-year survival, is lacking [10]. Moreover, the efficacy of dexamethasone in patients not requiring mechanical ventilation, particularly those needing only oxygen therapy, remains controversial [11].

This study aims to address these gaps by evaluating differences in short-term (28-day) and long-term (1-year) mortality outcomes associated with dexamethasone use in COVID-19 patients through a large-scale propensity score-matched analysis. The MIMIC-IV database, updated to version 3.0, includes extensive clinical data from large U.S. teaching hospitals during the COVID-19 pandemic and extends follow-up to 1 year. By employing propensity score matching and multivariate adjustments, we ensure comparability between the dexamethasone and non-dexamethasone groups in terms of demographic and clinical characteristics, thereby providing a more accurate assessment of its effectiveness. This study not only contributes new evidence on the long-term outcomes of dexamethasone but also offers fresh perspectives on optimizing treatment strategies for COVID-19 patients, particularly regarding dosing and respiratory support choices.

Methods

Study design and data source

This study is a retrospective cohort analysis using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (v3.0) [12]. The database contains comprehensive clinical data on patients admitted to intensive care units (ICUs) at Beth Israel Deaconess Medical Center between 2008 and 2022, with updates that include data from the COVID-19 pandemic. All researchers involved in this study completed training on research ethics through the Collaborative Institutional Training Initiative (CITI) program.

Patient selection

From the 94,458 ICU admissions recorded in the MIMIC-IV v3.0 database, we identified COVID-19 patients based on ICD-10 codes. Patients were excluded if they: (1) were younger than 16 years, (2) had ICU stays less than 24 h, (3) had multiple ICU admissions (only first ICU stay was retained), or (4) received corticosteroids other than dexamethasone during their ICU stay.

To minimize confounding and selection bias, all patients underwent 1:1 propensity score matching (PSM) based on variables including age, gender, body mass index (BMI), race, comorbidities, and laboratory parameters. After matching, 288 patients who received dexamethasone were compared with 288 patients who did not receive dexamethasone. Propensity score matching ensured comparability between the two groups in terms of demographic and clinical characteristics, providing a reliable foundation for the subsequent efficacy analysis.

Data collection

Clinical data for all patients were extracted from the MIMIC-IV v3.0 database. The key variables collected included demographic characteristics (age, gender, BMI, and race), disease severity scores (SOFA and APACHE III), and comorbidities including type 2 diabetes (T2DM), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and immunocompromised status (defined as organ transplantation, immunosuppressive therapy, solid tumors, or hematologic malignancies). Concomitant COVID-19 treatments were documented, specifically the use of antiviral therapy (Remdesivir) and immunomodulators (Baricitinib and Tocilizumab). Laboratory parameters were gathered, including complete blood count (white blood cell count, platelet count), biochemical parameters (lactate levels),

and respiratory parameters (PaO2/FiO2 ratio). Additionally, the types of respiratory support provided were recorded, categorized as oxygen therapy, non-invasive ventilation (NIV), and invasive mechanical ventilation (IMV).

Dexamethasone use

Dexamethasone use was the primary intervention variable in this study. Data on whether dexamethasone was administered after ICU admission for COVID-19 were collected.

Outcomes

The primary outcomes of this study were all-cause mortality at 28 days and 1 year after ICU treatment.

Statistical analysis

All statistical analyses were performed using R version 4.3.1. Continuous variables were presented as means with standard deviations or medians with interquartile ranges, depending on their distribution. Categorical variables were presented as frequencies and percentages. Differences between the dexamethasone and non-dexamethasone groups were assessed using Student's t-test or Mann-Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables, as appropriate. The primary outcomes of 28-day and 1-year mortality were analyzed using Kaplan-Meier survival curves, and differences between groups were assessed with the log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality, adjusting for potential confounders not fully addressed by propensity score matching. For all analyses, a two-sided p-value <0.05 was considered statistically significant.

Results

After propensity score matching, 576 COVID-19 patients were analyzed (288 in each group), with comparable baseline characteristics and comorbidities between groups except for BMI ($P=0.004$), as shown in Table 1. The dexamethasone group presented higher severity scores (APACHE III and SOFA, both $P<0.05$) and more severe respiratory impairment with lower P/F ratios ($P<0.001$) and higher NIV usage ($P<0.001$). This group also received more concurrent COVID-19 therapies, including Remdesivir and Tocilizumab (both $P<0.001$). Notably, the dexamethasone group demonstrated lower rates of multidrug-resistant infections ($P=0.038$) and 28-day mortality ($P=0.034$), with a trend toward lower 1-year mortality ($P=0.084$).

As shown in Table 2; Fig. 1, the dexamethasone group showed lower 28-day mortality risk compared to the non-dexamethasone group (crude HR 0.67, 95% CI 0.47–0.96, $P=0.028$; adjusted HR 0.67, 95% CI 0.46–0.99, $P=0.045$). This survival benefit extended to 1-year follow-up (adjusted HR 0.66, 95% CI 0.47–0.92, $P=0.014$).

Subgroup analysis stratified by respiratory support revealed varying treatment effects. In patients receiving oxygen therapy alone, dexamethasone showed no significant survival advantage at either 28 days (adjusted HR 0.73, 95% CI 0.33–1.62, $P=0.433$) or 1 year (adjusted HR 1.13, 95% CI 0.66–1.93, $P=0.650$). In contrast, significant survival benefits were observed in the NIV group at both 28 days (adjusted HR 0.15, 95% CI 0.05–0.42, $P<0.001$) and 1 year (adjusted HR 0.14, 95% CI 0.06–0.35, $P<0.001$), although the limited sample size warrants further investigation. For IMV patients, dexamethasone also demonstrated survival benefits at both 28 days (adjusted HR 0.62, 95% CI 0.39–0.99, $P=0.045$) and 1 year (adjusted HR 0.73, 95% CI 0.55–0.98, $P=0.040$). The interaction analysis confirmed these differential effects ($P=0.001$ at 28 days and $P=0.004$ at 1 year).

Kaplan-Meier analysis further supported these findings, showing higher survival rates in the dexamethasone group at both 28 days ($P=0.027$, Fig. 2) and 1 year ($P=0.057$, Fig. 3), with the survival advantage being particularly pronounced in the early months.

Further exploratory analyses of dose-response relationship and timing of administration showed no significant impact on either 28-day or 1-year mortality (all $P>0.05$), as shown in the supplementary figures and tables.

Discussion

This retrospective cohort study, based on the MIMIC-IV database, analyzed 576 confirmed COVID-19 ICU patients (288 in each group after propensity score matching) to evaluate the impact of dexamethasone on short-term (28-day) and long-term (1-year) mortality. We found that dexamethasone treatment was associated with reduced mortality at both 28 days (adjusted HR 0.67, 95% CI 0.46–0.99, $P=0.045$) and 1 year (adjusted HR 0.66, 95% CI 0.47–0.92, $P=0.014$). More importantly, subgroup analyses revealed differential treatment effects by respiratory support type (P for interaction=0.011 at 28 days and 0.004 at 1 year), with the most pronounced benefit observed in patients receiving NIV or IMV. These findings suggest that dexamethasone provides substantial protection for both short-term and long-term outcomes in hospitalized COVID-19 patients, particularly those requiring advanced respiratory support.

The association between dexamethasone and COVID-19 outcomes has been the subject of numerous studies, with evidence showing that dexamethasone, as a corticosteroid, can reduce mortality in hospitalized COVID-19 patients requiring respiratory support. The RECOVERY trial, the largest randomized controlled trial to date, demonstrated that dexamethasone significantly reduced

Table 1 Baseline Characteristics of the Propensity Score-Matched Cohort

Variable	PSM cohort		*P* value
	Non-dexamethasone, N = 288	Dexamethasone, N = 288	
Age, Median (Mean ± SD)	64.7 ± 17.0	63.3 ± 15.5	0.283
Gender, n (%)			0.270
Female	124 (43.1)	111 (38.5)	
Male	164 (56.9)	177 (61.5)	
BMI, Median (Mean ± SD)	30.4 ± 6.5	32.0 ± 6.9	0.004
Race, n (%)			0.561
White	119 (41.3)	122 (42.4)	
Black, Asian, or Hispanic	83 (28.8)	91 (31.6)	
other	86 (29.9)	75 (26)	
T2dm, n (%)			0.601
No	189 (65.6)	183 (63.5)	
Yes	99 (34.4)	105 (36.5)	
CKD, n (%)			0.99
No	239 (83)	239 (83)	
Yes	49 (17)	49 (17)	
COPD, n (%)			0.897
No	254 (88.2)	255 (88.5)	
Yes	34 (11.8)	33 (11.5)	
Immunosuppressant, n (%)			0.540
No	274 (95.1)	277 (96.2)	
Yes	14 (4.9)	11 (3.8)	
Apsiii, (Mean ± SD)	45.9 ± 19.3	50.1 ± 23.3	0.019
Sofa, (Mean ± SD)	4.8 ± 3.0	5.5 ± 3.9	0.023
White blood cell, Median (IQR)	10.1(7.3 − 13.7) ± 6.9	9.3(6.4–13.5)	0.061
Platelet, (Mean ± SD)	230.0 ± 101.1	240.6 ± 92.8	0.192
Lactate, Median (IQR)	1.6(1.2–2.0)	1.7(1.4–2.0)	0.229
P/F, Median (IQR)	132.2(89.8–212.0)	109.3(72.9–140.3)	< 0.001
Remdesivir, n (%)			< 0.001
No	271 (94.1)	210 (72.9)	
Yes	17 (5.9)	78 (27.1)	
Baricitinib, n (%)			0.176
No	286 (99.3)	281 (97.6)	
Yes	2 (0.7)	7 (2.4)	
Tocilizumab, n (%)			< 0.001
No	273 (94.8)	221 (76.7)	
Yes	15 (5.2)	67 (23.3)	
Respiratory support, n (%)			< 0.001
Oxygen	111 (41.1)	62 (21.5)	
NIV	18 (6.7)	79 (27.4)	
IMV	141 (52.2)	147 (51.1)	
MDR Bacteria and Invasive Fungal Infections, n (%)			0.038
No	280 (97.2)	287 (99.7)	
Yes	8 (2.8)	1 (0.3)	
28-day mortality, n (%)			0.034
Alive	215 (74.7)	236 (81.9)	
Death	73 (25.3)	52 (18.1)	
1-year mortality, n (%)			0.084
Alive	192 (66.7)	211 (73.3)	
Death	96 (33.3)	77 (26.7)	

Table 2 Cox Regression Results for Short-Term (28-Day) and Long-Term (1-Year) Mortality

Subgroup	Time Point	Crude HR (95% CI)	Crude *P* value	Adjusted HR (95% CI)[a]	Adjusted *P* value
Oxygen	28 days	1.3 (0.60–2.82)	0.512	0.73 (0.33–1.62)	0.433
	1 year	1.28 (0.76–2.15)	0.360	1.13 (0.66–1.93)	0.650
NIV	28 days	0.17 (0.06–0.44)	< 0.001	0.15 (0.05–0.42)	< 0.001
	1 year	0.24 (0.10–0.56)	< 0.001	0.14 (0.06–0.35)	< 0.001
IMV	28 days	0.71 (0.45–1.12)	0.138	0.62 (0.39–0.99)	0.045
	1 year	0.81 (0.60–1.07)	0.140	0.73 (0.55–0.98)	0.040
All patients	28 days	0.67(0.47–0.96)	0.028	0.67 (0.46–0.99)	0.045
	1 year	0.75(0.55–1.01)	0.057	0.66 (0.47–0.92)	0.014

a Adjusted for BMI, P/F ratios, Apsiii, Sofa, Remdesivir, Tocilizumab

P value for interaction: 28 days, *P*=0.001; 1 year, *P*=0.004

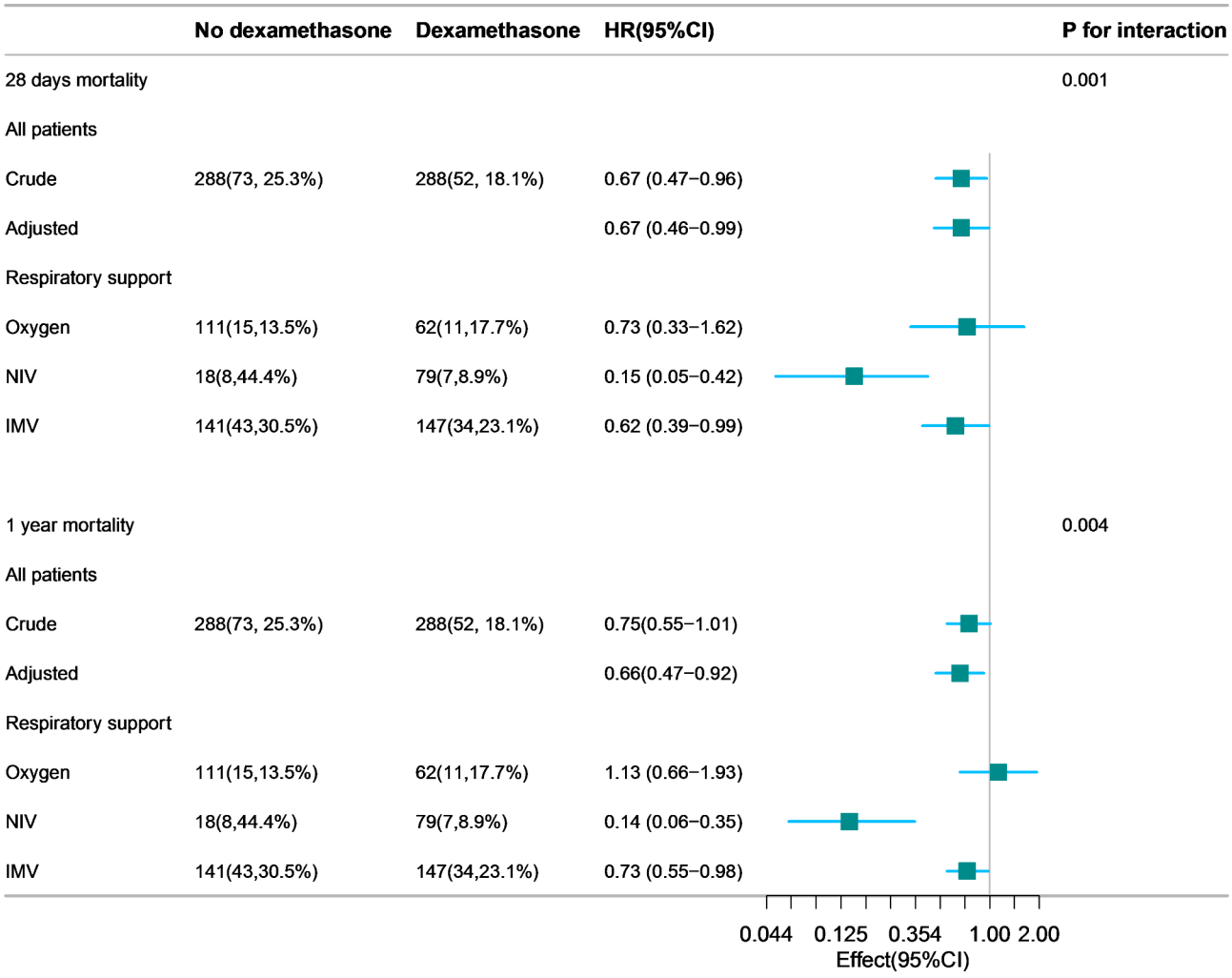

Fig. 1 Effect of dexamethasone on 28-day and 1-year mortality, according to respiratory support

28-day mortality in patients requiring mechanical ventilation or oxygen support, consistent with the results of our study [5]. In our analysis, we also observed significant reductions in 28-day mortality for patients receiving IMV and NIV, further supporting the clinical benefits of dexamethasone in critically ill patients. Moreover, our study extended the analysis to long-term survival, showing that the protective effects of dexamethasone persisted during the 1-year follow-up. Notably, dexamethasone has shown substantial efficacy in mitigating the severe inflammatory response associated with COVID-19. A study from India focused on the adjunctive use of dexamethasone in severe COVID-19 patients, revealing that it effectively reduced inflammation markers, such as interleukin-6, D-dimer,

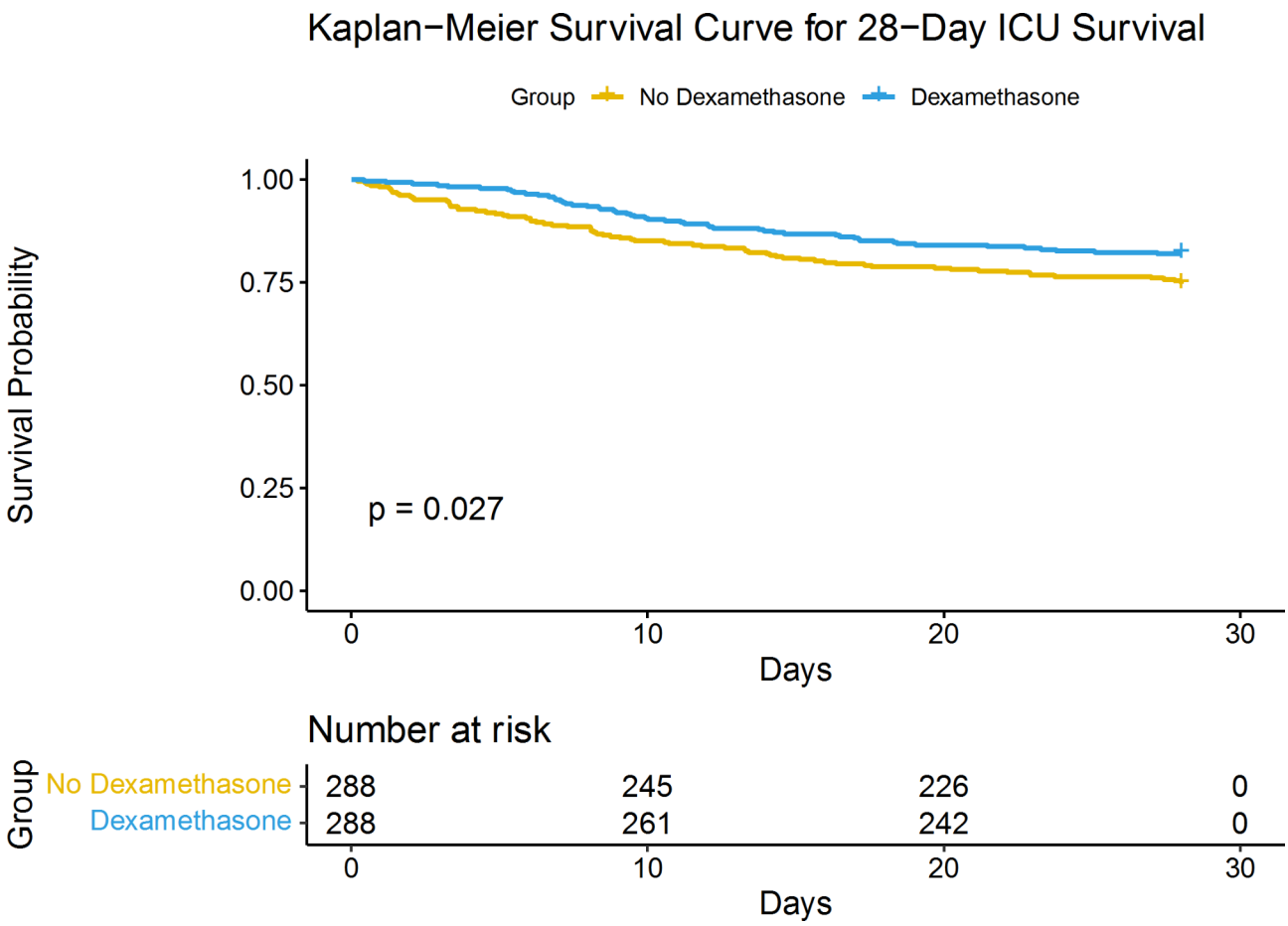

Fig. 2 Kaplan-Meier survival curve for 28-day ICU survival by dexamethasone use in COVID-19 patients

and ferritin levels [13]. In our study, despite higher lactate levels and more severe respiratory impairment in the dexamethasone group, the treatment significantly lowered mortality, closely related to its anti-inflammatory effects. Additionally, meta-analyses of several randomized trials further validated the reduction in all-cause mortality in critically ill COVID-19 patients requiring respiratory support with corticosteroids, including dexamethasone, aligning with the survival benefits we observed in both short- and long-term outcomes [7, 14, 15].

It is noteworthy that while many studies have affirmed the benefits of dexamethasone in critically ill COVID-19 patients, some have questioned its early use. A multicenter cohort study found that early dexamethasone administration reduced the risk of respiratory failure and mechanical ventilation in non-ventilated COVID-19 patients and shortened hospital stays [16, 17]. However, our study showed no significant difference in survival outcomes between early dexamethasone use (within 48 h) and delayed administration, in both short-term and long-term survival rates. This result contradicts some literature findings and may be attributable to differences in baseline characteristics, disease severity, or the timing of dexamethasone administration. Additionally, the RECOVERY trial cautioned against the use of dexamethasone in patients with mild-to-moderate pulmonary symptoms due to potential adverse effects [5]. Our study also supports this, as dexamethasone did not demonstrate significant survival benefits in patients receiving only oxygen therapy, suggesting that its use in less severe cases should be approached with caution.

The choice of dexamethasone dosage varies among studies. A very recent study by Zhang et al. demonstrated that high-dose corticosteroids were more effective in reducing inflammatory factors and shortening body temperature recovery time in severe COVID-19 pneumonia, suggesting the potential benefits of higher doses in selected patients [18]. However, the standard dosage used in the RECOVERY trial was 6 mg daily, administered either orally or intravenously for up to 10 days or until hospital discharge [5]. Other studies have explored the effects of higher doses of dexamethasone, but no additional survival benefits were observed compared to the standard dose [19–21]. In fact, higher doses may increase the risk of immunosuppression, rendering patients more

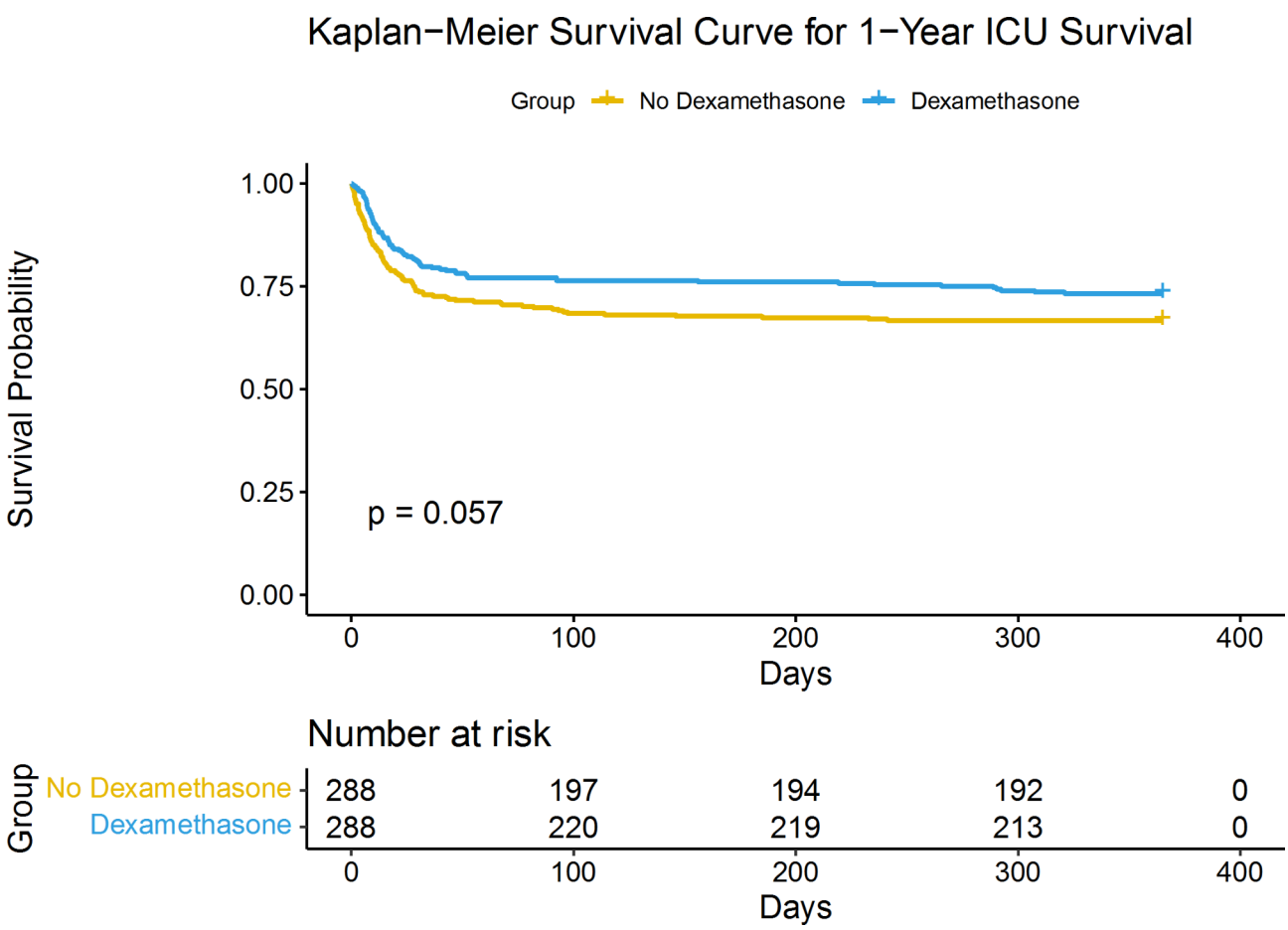

Fig. 3 Kaplan-Meier survival curve for 1-year ICU survival by dexamethasone use in COVID-19 patients

susceptible to secondary infections. Current clinical guidelines recommend low-dose (6 mg) dexamethasone as the standard treatment for critically ill COVID-19 patients, while its use in less severe cases requires more caution. Overall, while dexamethasone has shown positive effects in reducing mortality and inflammation in critically ill patients, the optimal timing and dosing of the drug still need further investigation.

This study provides further evidence supporting the widespread use of dexamethasone in critically ill COVID-19 patients, especially those requiring NIV or IMV. By reducing both 28-day and 1-year mortality, dexamethasone demonstrated significant survival benefits in both short-term and long-term prognoses. These findings are consistent with existing literature, further confirming the efficacy of dexamethasone in combating the severe inflammatory response associated with COVID-19. In patients requiring respiratory support, dexamethasone improves outcomes by preventing further disease progression through the suppression of hyperinflammatory responses. This finding offers clear guidance for clinicians in managing critically ill COVID-19 patients, particularly when making treatment decisions regarding oxygen support, where dexamethasone can serve as a first-line therapy. Furthermore, the relatively low cost and widespread availability of dexamethasone make it a feasible and effective treatment option globally. Particularly in resource-limited healthcare settings, dexamethasone's use can significantly reduce the medical burden and mortality rates in critically ill patients. While the efficacy of dexamethasone has been established in severe cases, its use in milder cases still requires cautious evaluation. Thus, careful patient selection and personalized treatment strategies are crucial in the treatment of COVID-19.

Several limitations should be acknowledged in this study. First, due to its retrospective design, although propensity score matching was employed to minimize confounding factors, unmeasured biases may still exist. Particularly, some antiviral medications not recorded in the MIMIC-IV database could not be included in our analysis, potentially affecting the results. Second, the MIMIC-IV v3.0 database lacks imaging data, preventing us from analyzing the correlation between thorax CT classifications, disease severity, and dexamethasone dosing. Third, while we conducted exploratory analyses

on dosing and timing of dexamethasone administration, this study primarily focused on validating the real-world effectiveness of dexamethasone on short-term and long-term outcomes in COVID-19 patients. Additionally, as the data were derived from a single healthcare system in the United States, the generalizability of our findings to other healthcare settings requires further validation. The relatively small sample size in certain subgroups, particularly patients receiving NIV, also limited our ability to draw more definitive conclusions about treatment effects in these populations.

To address these limitations, future research should further explore the optimal timing and dosage of dexamethasone in the treatment of COVID-19, particularly in different patient severity groups. Based on our findings of a dose-response relationship, future clinical trials should more closely evaluate the effects of varying doses of dexamethasone on improving prognosis and reducing side effects. Additionally, more research is needed to assess the role of dexamethasone in combination therapies, such as its use with antiviral drugs or immune modulators, to determine whether these combinations can further enhance patient survival and accelerate recovery. Future studies should also focus on the effectiveness of dexamethasone in different healthcare systems worldwide. Particularly in low- and middle-income countries, dexamethasone, as an inexpensive and accessible drug, may have greater clinical potential in reducing mortality among critically ill COVID-19 patients. Large-scale global multicenter clinical trials will provide stronger evidence for its use across diverse healthcare settings.

Conclusion

This retrospective study demonstrates that dexamethasone treatment significantly reduces both short-term and long-term mortality in hospitalized COVID-19 patients, particularly in those receiving NIV or IMV. These findings support the use of dexamethasone in severe COVID-19 patients requiring advanced respiratory support.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10216-3.

Supplementary Material 1: Impact of Early vs. Delayed Dexamethasone Administration on 28-day and 1-year

Supplementary Material 2: RCS Curve Analysis of Dexamethasone Dose and 28-day Mortality

Supplementary Material 3: RCS Curve Analysis of Dexamethasone Dose and 1-year Mortality

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Author contributions
Jian Zhao, Hui Hua Jiang, Hong Hong Wan, Dan Liu, and Yi Zhao contributed equally to this work. They were responsible for the conception, design, and execution of the study, as well as data collection and analysis. Yan Qing Chen and Yuan Zhuo Chen supervised the project, provided critical revisions, and guided the writing of the manuscript. All authors read and approved the final version of the manuscript.

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Data availability
The datasets are available in the physionet (https://physionet.org/content/mimiciv/0.4/).

Declarations

Ethics approval and consent to participate
The MIMIC-IV database was approved by the Institutional Review Boards of Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA). Informed consent was obtained for the original data collection. The requirement for individual patient consent was waived as the project did not impact clinical care and all protected health information was de-identified.

Consent for publication
Non-applicable.

Competing interests
The authors declare no competing interests.

Clinical trial registration
Non-applicable.

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