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Cohort Study

In-hospital mortality in SARS-CoV-2 stratified by the use of corticosteroid

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ABSTRACT

Objective: To investigate COVID-19 related mortality according to the use of corticosteroid therapy.
Design: Retrospective cohort study.
Setting: Two tertiary hospitals in Kuwait.
Participants: Overall, 962 patients with confirmed SARS-CoV-2 infection, were stratified according to whether they were treated with corticosteroids (dexamethasone or methylprednisolone). The mean age of the patients was 50.2 ± 15.9 years and 344/962 (35.9%) were female.
Main outcome measures: In-hospital mortality and cumulative all-cause mortality.
Results: Compared to non-corticosteroid therapy patients, corticosteroid therapy patients had a higher prevalence of hypertension, diabetes mellitus, cardiovascular disease, chronic lung disease, and chronic kidney disease; a longer hospital stay (median [IQR]: 17.0 [5.0–57.3] days vs 14.0 [2.0–50.2] days); and a higher in-hospital mortality (51/199 [25.6%] vs 36/763 [4.7%]). Logistic regression analysis showed a higher in-hospital mortality in the corticosteroid group (adjusted odds ratio [aOR]: 4.57, 95% confidence interval [CI]: 2.64–8.02, $p < 0.001$). Cox proportional hazards regression showed that corticosteroid use was a significant predictor of mortality (hazard ratio [HR]: 3.96, $p < 0.001$).
Conclusions: In-hospital mortality in patients with SARS-CoV-2 on corticosteroid therapy was 4.6 times higher than in those without corticosteroid therapy.

1. Introduction

In coronavirus disease (COVID-19), corticosteroid use has been reported to be associated with improved clinical outcomes but not mortality. [1]. In both critically ill and non-critically ill COVID-19 patients, corticosteroid use has no clear mortality benefit. [2,3]. In one study, higher mortality rates were reported in COVID-19 patients who were treated with corticosteroids. [4]. Promising mortality benefits were observed with the administration of dexamethasone in hospitalised COVID-19 patients. [5]. The rate of intensive care unit (ICU) admissions

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was reduced by using corticosteroids in COVID-19 patients. [6]. A two-fold increase in mortality was reported in COVID-19 patients who were kept on steroids. [7]. The use of corticosteroids can result in the persistence of viral RNA in the blood. [8]. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) study reported that dexamethasone might even cause harm to COVID-19 patients not requiring oxygen as a part of the treatment protocol. [5]. A more extended hospital stay was reported in COVID-19 patients who were not on dexamethasone therapy. [9]. No mortality benefit was seen when tocilizumab and corticosteroid were used for treating COVID-19, but without corticosteroid, tocilizumab administration showed a mortality benefit. [10].

2. Materials and methods

2.1. Study design and participants

This retrospective cohort study included patients, both Kuwaitis and non-Kuwaitis, aged 18 years and older who were hospitalised with COVID-19 (Fig. 1). Data were extracted from the electronic medical records of two Kuwaiti tertiary care hospitals: Al Adan General Hospital and Jaber Al-Ahmed Hospital. [11–15]. For data entry, an electronic case record form (CRF) was employed. A positive reverse-transcription polymerase chain reaction (RT-PCR) utilizing samples of nasopharyngeal swab confirmed the presence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Our study was in line with the STROCSS criteria. [16]. It was registered with the research registry under a unique identifying number (UIN): researchregistry8014. [17]. The Ministry of Health in Kuwait standardized the care of all patients according to protocol. The research protocol was authorized by Kuwait's Ministry of Health's Standing Committee for Health and Medical Research Coordination (Institutional Review Board number 2020/1422). Because the study design was retrospective in nature, the necessity for informed consent was waived.

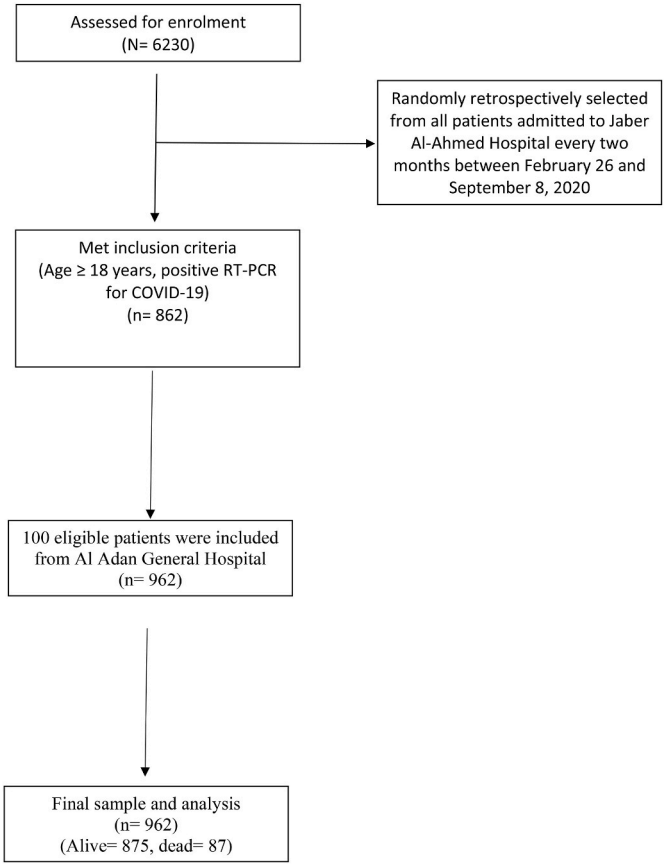

Fig. 1. Study flowchart.

2.2. Definitions

The primary outcome measured was COVID-19-related death, as defined by ICD 10 code U07.1. Secondary outcome measures included length of hospital stay, and the need for ICU admission due to COVID-19. Corticosteroid therapy was defined as receiving dexamethasone or methylprednisolone during the hospital stay. There were 146 patients managed with methylprednisolone at a minimum dose of 0.5–1 mg/kg/day. Fifty-three patients were treated with dexamethasone at a daily dose of 6–12 mg. Twenty-two patients were switched from dexamethasone to methylprednisolone or vice versa. Corticosteroid therapy was administered intravenously. Chronic lung disease was defined as a confirmed diagnosis of obstructive or restrictive lung disease. An immunocompromised patient was defined as a patient on immunosuppressive treatment. The need for oxygen was classified into two groups: high and low oxygen requirement. High-flow oxygen, non-invasive ventilation, invasive ventilation, and extracorporeal membrane oxygenation (ECMO) were grouped under the high oxygen requirement category; and patients who needed oxygen via a nasal cannula or a non-rebreather mask were included in the low oxygen requirement group. Clinical and laboratory variables collected were as follows: sociodemographic characteristics, sources of transmission, co-morbidities, clinical presentation, laboratory results, medications administered in the hospital, and duration of ICU and in-hospital stay.

2.3. Statistical analysis

Descriptive statistics were used to summarise the data. Frequency, percentages, means with standard deviations, and medians with interquartile ranges were used as summary measures. Pearson's chi-square test was used to check the association between use of corticosteroid therapy category (yes, no) and other study variables. Multivariable logistic regression was used to check the impact of corticosteroid therapy, age, fever, statin use, and tocilizumab on mortality. Cox proportional hazards regression and Kaplan-Meier survival analysis were used to determine the effect of corticosteroid therapy on mortality. P-values <0.05 were considered statistically significant. SPSS version 27 (IBM Corp., Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analysis of the data. [18].

2.4. Patient and public involvement

Patients were not involved in the design, recruitment, conduct, and reporting of this research.

3. Results

A total of 962 COVID-19 patients were included in the study, of whom 344 (35.9%) were female and 615 (64.1%) were male. Their baseline characteristics are shown in Table 1. Among the 962 patients, 75.6% had never smoked. The most common sources of SARS-COV-2 infection were the community (346, 40.2%) or contact (386, 44.9%). The most common source of SARS-COV-2 infection in the corticosteroid therapy group was community transmission (104, 57.1%), while in the non-corticosteroid therapy group, the most common source of SARS-COV-2 infection was a known contact (315, 46.5%). The prevalence of hypertension, diabetes mellitus (DM), cardiovascular disease (CVD), chronic lung disease (CLD), and chronic kidney disease (CKD) was higher in the corticosteroid therapy group than in the non-corticosteroid therapy group. In the non-corticosteroid group, a higher proportion of patients had COVID-19 pneumonia (335, 43.9%), while a higher proportion of patients in the corticosteroid group had acute respiratory distress syndrome (ARDS) secondary to COVID-19 (84, 42.2%). Almost

Table 1
Baseline characteristics of the COVID-19 patients in the corticosteroid therapy and non-corticosteroid therapy groups.

	All	Non-corticosteroid Rx	Corticosteroid Rx	*p*-value	N
	N = 962	*N* = 763	*N* = 199		
Age, mean ± SD, years	50.2 (15.9)	48.4 (15.8)	57.1 (14.3)	<0.001	962
BMI, mean ± SD, kg/m^2	29.0 (6.18)	28.7 (6.13)	30.4 (6.25)	0.010	606
Sex:				0.725	959
Female	344 (35.9%)	270 (35.5%)	74 (37.2%)		
Male	615 (64.1%)	490 (64.5%)	125 (62.8%)		
Smoking:				0.047	270
Current Smoker	38 (14.1%)	33 (16.0%)	5 (7.81%)		
Ex-Smoker	28 (10.4%)	17 (8.25%)	11 (17.2%)		
Never Smoked	204 (75.6%)	156 (75.7%)	48 (75.0%)		
Source of transmission:				<0.001	860
Community	346 (40.2%)	242 (35.7%)	104 (57.1%)		
Contact	386 (44.9%)	315 (46.5%)	71 (39.0%)		
Healthcare worker	22 (2.56%)	21 (3.10%)	1 (0.55%)		
Hospital acquired	11 (1.28%)	6 (0.88%)	5 (2.75%)		
Imported	95 (11.0%)	94 (13.9%)	1 (0.55%)		
Hypertension	324 (33.7%)	221 (29.0%)	103 (51.8%)	<0.001	962
DM	335 (34.8%)	233 (30.5%)	102 (51.3%)	<0.001	962
CVD	79 (8.21%)	54 (7.08%)	25 (12.6%)	0.018	962
Chronic lung disease	87 (9.04%)	58 (7.60%)	29 (14.6%)	0.004	962
Chronic kidney disease	43 (4.47%)	25 (3.28%)	18 (9.05%)	0.001	962
Immunocompromised host	16 (1.66%)	10 (1.31%)	6 (3.02%)	0.115	962
Pneumonia	527 (54.8%)	335 (43.9%)	192 (96.5%)	<0.001	962
ARDS	140 (14.6%)	56 (7.34%)	84 (42.2%)	<0.001	962
ICU admission	149 (15.5%)	66 (8.65%)	83 (41.7%)	<0.001	962
ICU length of stay (days) IQR	13.0 [1.75;63.8]	11.0 [2.00;58.8]	14.5 [1.02;65.8]	0.121	151
Hospital length of stay (days) IQR	15.0 [2.00;52.0]	14.0 [2.00;50.2]	17.0 [5.00;57.3]	<0.001	950
Mortality	87 (9.04%)	36 (4.72%)	51 (25.6%)	<0.001	962

The values are n (%) unless specified otherwise.
ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, coronavirus disease; CVD, cardiovascular disease; DM, diabetes mellitus; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

42% of the participants in the corticosteroid therapy group were admitted to an ICU compared to 9% of the non-corticosteroid therapy group. The median length of hospital stay was 17.0 days (interquartile range [IQR]: 5.0–57.3 days) in the corticosteroid therapy group, and 14.0 (IQR: 2.0–50.2 days) in the non-corticosteroid therapy group. The overall mortality rate was 9.04% (n = 87) and was higher in the corticosteroid therapy group (25.6%, n = 51) than in the non-corticosteroid therapy group (4.72%, n = 36).

Table 2 shows the signs and symptoms of the patients in the corticosteroid and non-corticosteroid therapy groups. The proportions of asymptomatic patients among the corticosteroid- and non-corticosteroid therapy groups were 3.0% (n = 6) and 19.5% (n = 149), respectively.

Table 3 shows the laboratory parameters of patients in the corticosteroid and non-corticosteroid therapy groups. Patients in the corticosteroid therapy group had significantly lower haemoglobin levels, lymphocyte counts, and albumin than patients in the non-corticosteroid therapy group. Conversely, patients in corticosteroid group had significantly higher platelets, white blood cell (WBC) and neutrophil counts, and creatinine, lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin, D-Dimer, high-sensitivity (HS) serum troponin, ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and direct bilirubin levels than patients in non-corticosteroid group.

Table 4 shows the medication taken by patients in the corticosteroid and non-corticosteroid therapy groups during their hospital stay. A higher proportion of patients in the non-steroid therapy group received antibiotics, therapeutic anticoagulation, tocilizumab, angiotensin II receptor blockers (ARBs), and statins. More patients in the corticosteroid therapy group had a high oxygen requirement.

The logistic regression results (Table 5) showed that corticosteroid therapy, age, and tocilizumab therapy had a significant impact on cumulative all-cause mortality ($p < 0.001$). The finding shows that the patients receiving corticosteroid therapy had higher mortality than the patients who did not receive the therapy (adjusted odds ratio [aOR]:

Table 2
Signs and symptoms of the COVID-19 patients in the corticosteroid therapy and non-corticosteroid therapy groups.

	All	Non-corticosteroid Rx	Corticosteroid Rx	*p*-value	N
	N = 962	N = 763	N = 199		
Asymptomatic	155 (16.1%)	149 (19.5%)	6 (3.02%)	<0.001	962
Headache	100 (10.4%)	79 (10.4%)	21 (10.6%)	>0.990	962
Sore throat	93 (9.67%)	82 (10.7%)	11 (5.53%)	0.037	962
Fever	547 (56.9%)	402 (52.7%)	145 (72.9%)	<0.001	962
Dry cough	459 (47.7%)	332 (43.5%)	127 (63.8%)	<0.001	962
Productive cough	68 (7.07%)	54 (7.08%)	14 (7.04%)	>0.990	962
SOB	309 (32.1%)	188 (24.6%)	121 (60.8%)	<0.001	962
Fatigue or myalgia	216 (22.5%)	155 (20.3%)	61 (30.7%)	0.003	962
Diarrhoea	113 (11.7%)	86 (11.3%)	27 (13.6%)	0.440	962
Nausea	60 (6.24%)	44 (5.77%)	16 (8.04%)	0.309	962
Vomiting	59 (6.13%)	43 (5.64%)	16 (8.04%)	0.274	962
Change of taste or smell	34 (3.53%)	25 (3.28%)	9 (4.52%)	0.527	962

The values are n (%) unless specified otherwise.
COVID-19, coronavirus disease; SOB, shortness of breath.

Table 3
Laboratory parameters of the COVID-19 patients in the corticosteroid therapy and non-corticosteroid therapy groups.

	All	Non-corticosteroid Rx	Corticosteroid Rx	*p*-value	N
	N = 951	N = 753	N = 198		
Haemoglobin (g/L)	127 [125;129]	129 [126;131]	120 [113;125]	<0.001	951
Platelets (10^9/L)	254 [244;265]	249 [238;259]	281 [256;293]	0.025	950
WBC (10^9/L)	6.70 [6.50;7.00]	6.40 [6.20;6.60]	8.95 [7.90;10.2]	<0.001	949
Neutrophils count	4.14 [4.00;4.40]	3.80 [3.60;4.00]	7.20 [6.40;8.40]	<0.001	948
Lymphocytes count	1.40 [1.40;1.50]	1.60 [1.50;1.60]	0.80 [0.75;0.90]	<0.001	948
Creatinine (umol/L)	76.0 [75.0;78.0]	75.0 [73.0;77.0]	84.5 [77.0;94.0]	<0.001	945
LDH (IU/L)	305 [290;322]	272 [251;293]	359 [338;380]	<0.001	641
CRP (mg/L)	49.0 [38.0;56.8]	28.0 [22.0;34.0]	106 [87.2;119]	<0.001	907
Procalcitonin (ng/mL)	0.09 [0.08;0.10]	0.07 [0.07;0.08]	0.49 [0.33;1.20]	<0.001	609
D-Dimer (ng/mL)	360 [320;402]	286 [259;322]	608 [507;707]	<0.001	617
25 (OH) Vitamin D (nmol/L)	41.0 [37.0;44.0]	39.0 [37.0;44.0]	43.5 [32.0;66.0]	0.395	239
Troponin I HS (ng/L)	9.00 [7.00;11.0]	7.00 [6.00;9.00]	14.0 [10.0;20.0]	<0.001	331
Ferritin (ng/mL)	449 [398;496]	384 [345;426]	655 [514;800]	<0.001	595
Creatinine kinase (IU/L)	88.0 [60.0;160]	81.0 [56.0;178]	105 [59.0;701]	0.359	33
ALT (IU/L)	33.0 [31.0;35.0]	31.0 [29.0;34.0]	42.0 [36.0;52.0]	<0.001	942
AST (IU/L)	33.0 [32.0;35.0]	31.0 [29.0;32.0]	46.0 [42.0;51.0]	<0.001	941
ALP (IU/L)	69.0 [67.0;72.0]	67.0 [65.0;70.0]	80.0 [74.0;90.0]	<0.001	939
GGT (IU/L)	36.5 [33.0;41.0]	31.0 [28.0;34.0]	77.5 [60.0;83.0]	<0.001	802
Albumin (g/L)	35.3 [35.0;35.9]	36.2 [35.9;36.9]	31.4 [29.9;32.0]	<0.001	940
T. Bilirubin (umol/L)	11.5 [11.0;11.8]	11.6 [11.1;11.9]	11.0 [10.0;12.0]	0.806	940
D. Bilirubin (umol/L)	2.60 [2.40;2.70]	2.50 [2.30;2.60]	3.00 [2.50;3.40]	0.001	926

The values are median [IQR].
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease; CRP, C-reactive protein; D. bilirubin, direct bilirubin; GGT, gamma-glutamyl transferase; HS, high-sensitivity; LDH, lactate dehydrogenase; T. bilirubin, total bilirubin; WBC, white blood cells.

Table 4
Medications administered to the COVID-19 patients in the corticosteroid therapy and non-corticosteroid therapy groups.

	All	Non-corticosteroid Rx	Corticosteroid Rx	*p*-value	N
	N = 962	N = 763	N = 199		
Antibiotics	443 (46.0%)	273 (35.8%)	170 (85.4%)	<0.001	962
Methylprednisolone	146 (15.2%)	0 (0.00%)	146 (73.4%)	<0.001	962
Dexamethasone	75 (7.80%)	0 (0.00%)	75 (37.7%)	<0.001	962
Vitamin C effervescent tablets	606 (63.0%)	481 (63.0%)	125 (62.8%)	>0.990	962
Therapeutic anticoagulation	302 (31.4%)	162 (21.2%)	140 (70.4%)	<0.001	962
Azithromycin	18 (1.87%)	7 (0.92%)	11 (5.53%)	<0.001	962
Vitamin D:				0.921	962
With Vit-D	334 (34.7%)	266 (34.9%)	68 (34.2%)		
Without Vit-D	628 (65.3%)	497 (65.1%)	131 (65.8%)		
Hydroxychloroquine	113 (11.7%)	98 (12.8%)	15 (7.54%)	0.052	962
Kaletra (lopinavir/ritonavir)	110 (11.4%)	85 (11.1%)	25 (12.6%)	0.662	962
Tocilizumab	17 (1.77%)	9 (1.18%)	8 (4.02%)	0.013	962
Hydrocortisone	22 (2.29%)	17 (2.23%)	5 (2.51%)	0.791	962
Current use of ACE inhibitors	87 (10.5%)	62 (9.52%)	25 (14.3%)	0.092	826
Current use of ARBs	110 (13.3%)	75 (11.4%)	35 (20.6%)	0.003	826
Current use of statins	219 (25.6%)	143 (21.3%)	76 (41.1%)	<0.001	855
Oxygen requirements:				<0.001	887
High oxygen requirement	139 (15.7%)	60 (8.70%)	79 (40.1%)		
Low oxygen requirements	249 (28.1%)	144 (20.9%)	105 (53.3%)		
None	499 (56.3%)	486 (70.4%)	13 (6.60%)		

The values are n (%), unless specified otherwise.
ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; COVID-19, coronavirus disease.

4.57, 95% confidence interval [CI]: 2.64–8.02, $p < 0.001$). The cumulative all-cause mortality rate was higher among patients who were taking tocilizumab (aOR: 15.26, 95% CI: 4.37–54.74, $p < 0.001$). Age (aOR: 1.06, 95% CI: 1.04–1.08, $p < 0.001$) had a significant impact on the cumulative all-cause mortality. Fever ($p = 0.136$) and current use of statins ($p = 0.136$) had no significant impact on the cumulative all-cause mortality.

A Kaplan-Meier survival probability plot shows the survival probability according to corticosteroid use (Fig. 2). The plot shows that in the initial and later periods, the cumulative probability of dying was higher among patients treated with corticosteroids. A Cox proportional hazards model was used to determine whether corticosteroid therapy had a significant effect on risk of mortality. The model results were significant ($LL = 38.71$, $df = 1$, $B = 1.38$, $SE = 0.22$, $HR = 3.96$, $p < 0.001$), indicating that corticosteroid therapy was an independent predictor of mortality and was associated with a fourfold increase in risk of death.

4. Discussion

The main finding of our study is that mortality was higher among patients who received corticosteroid therapy. In our study, approximately 21% of COVID-19 patients were treated with corticosteroids. Patients in the corticosteroid therapy group required a higher amount of oxygen than patients in the non-corticosteroid therapy group. Logistic regression analysis showed that corticosteroid therapy, age, and tocilizumab therapy were all independently associated with cumulative all-cause mortality. The primary source of SARS-COV-2 in this study was community-based or contact. Most patients in the corticosteroid therapy

Table 5
Logistic regression analysis of risk factors for in-hospital death in the overall study cohort.

		Alive	Dead	In-hospital mortality	
				Crude OR (95% CI, *p*-value)	Adjusted OR (95% CI, *p*-value)
Corticosteroid therapy	Yes	148 (74.4)	51 (25.6)	6.96 (4.40–11.11, p < 0.001)	4.57 (2.64–8.02, p < 0.001)
Age	Mean (SD)	48.9 (15.4)	63.5 (14.8)	1.06 (1.05–1.08, p < 0.001)	1.06 (1.04–1.08, p < 0.001)
Fever	Yes	485 (88.7)	62 (11.3)	1.99 (1.25–3.29, p = 0.005)	1.57 (0.88–2.90, p = 0.136)
Current use of statins	Yes	182 (83.1)	37 (16.9)	3.60 (2.20–5.92, p < 0.001)	1.58 (0.87–2.88, p = 0.136)
Tocilizumab therapy	Yes	7 (41.2)	10 (58.8)	16.10 (6.02–45.48, p < 0.001)	15.26 (4.37–54.74, p < 0.001)

The percentages are row percentages. The multivariable logistic regression analysis was conducted using the simultaneous method. The model was adjusted for corticosteroid therapy, age, fever, statins use, and tocilizumab use.
CI, confidence interval; OR, odds ratio; SD, standard deviation.

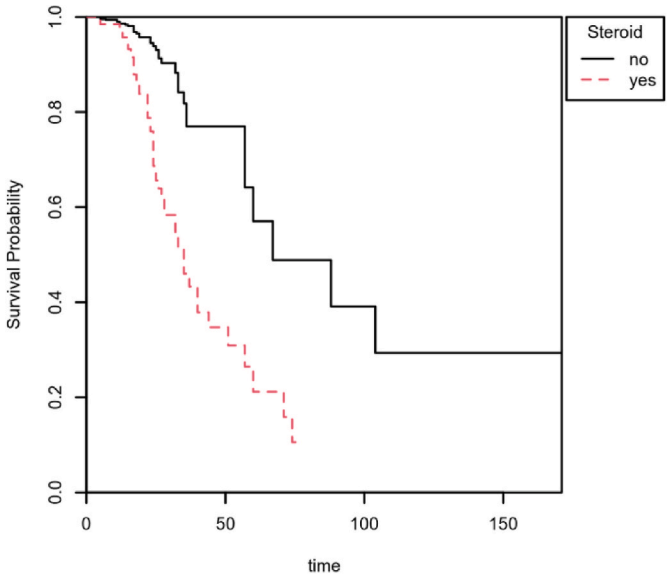

Fig. 2. Kaplan-Meier survival plot of mortality according to corticosteroid use in patients with coronavirus disease [COVID-19]. X-axis Days since admission.

group acquired SARS-COV-2 infection in the community. In contrast, patients in the non-corticosteroid therapy group were more likely to acquire SARS-COV-2 infection from a close contact.

A meta-analysis showed the benefit of corticosteroid use in terms of reduced requirement of invasive mechanical ventilation, and patients who were already on invasive mechanical ventilation could be weaned off early. [19]. In contrast, few studies have shown a benefit of corticosteroid use, especially when administered at a moderate dose for a shorter period. [20]. Studies have shown increasing rates of mortality with higher doses of corticosteroids. [21]. Another study showed that late initiation of corticosteroids in patients with COVID-19 had an increased mortality risk. [22]. Even with a short duration of corticosteroid use, all-cause mortality was high. [23]. In another study of 1461 hospitalised patients, corticosteroid use was associated with lower mortality among patients who stayed for more than 3 days. [24].

Complications from corticosteroid use are well known, including electrolyte imbalance, abnormal glycaemic status, and infections. [25–27]. The major setback in the use of corticosteroids in COVID-19 is associated with ARDS and acute lung injury. [28]. In COVID-19 patients with ARDS, early administration of dexamethasone has been shown to have a beneficial effect on the immune response. [29].

Many studies have reported that the use of corticosteroids ranges up to 70%, and patients on these treatments had worse clinical outcomes. [30]. Dexamethasone has no mortality benefit in patients with symptom onset of less than seven days. [5]. A systematic review and meta-analysis showed no mortality benefit with the use of corticosteroids when compared to those not on corticosteroids. [31]. A UK based study has shown a mortality benefit when corticosteroids are administered to patients on invasive mechanical ventilators. [32]. No in-hospital mortality benefits with corticosteroid use were observed in patients who did not require invasive mechanical ventilation. [5].

Initially, the WHO did not recommend the routine use of corticosteroids in patients with COVID-19 outside of clinical trials. [33]. The majority of the initial guidelines were against the use of corticosteroids in patients with COVID-19. [34]. Among the contrasting data on corticosteroid use in patients with COVID-19, a few guidelines recommend corticosteroid use in critical patients who require oxygen therapy. [35–37].

4.1. Limitations

This study included all patients admitted to the study hospitals with COVID-19 during the study period. Moreover, the high risk of COVID-19 related death in corticosteroids group could be in part a result of the baseline clinical characteristics. The prevalence of hypertension, DM, CVD, CLD, and CKD in the corticosteroids group was higher relative to the non-corticosteroids group; these baseline clinical characteristics were reported to be independent risk factors for COVID-19 related mortality in Kuwait. [14].

5. Conclusions

This study demonstrated that corticosteroid therapy was an independent predictor of in-hospital mortality in COVID-19 patients. Longer ICU stay was observed more frequently with the use of corticosteroids. More randomised trials are required to better understand the effect of corticosteroids on in-hospital mortality in COVID-19 patients with these baseline clinical characteristics.

Ethics approval statement

This study was approved by the Standing Committee for Coordination of Health and Medical Research at the Ministry of Health in Kuwait (Institutional Review Board number 2020/1422).

Patient consent statement

The requirement for patient consent was waived because of the retrospective observational study design.

Permission to reproduce material from other sources

No material from other sources was included in this study.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

Funding statement

No funding was received for this study.

Authors' contributions

MAR designed the study. NAO, MAR, and RR participated in data analysis and manuscript preparation. AAS and JP performed the statistical analysis and reviewed the manuscript. The remaining authors collected the data. All authors had access to the data and took responsibility for the integrity and accuracy of data analysis. All authors have read and approved the manuscript.

Registration of research studies

1 Name of the registry: Research Registry.
2 Unique Identifying number or registration ID: researchregistry8014.
3 Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/62ab5dd554853e001e097baf/

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Abbreviations

ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
aOR	Adjusted odds ratio
ARBs	Angiotensin II receptor blockers
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
CI	Confidence interval
CKD	Chronic kidney disease
COVID-19	Coronavirus disease
CRF	Case record form
CRP	C-reactive protein
CVD	Cardiovascular disease
DM	Diabetes mellitus
GGT	Gamma-glutamyl transferase
HR	hazard ratio
HS	high-sensitivity
ICU	Intensive care unit
IQR	interquartile range
LDH	Lactate dehydrogenase
RECOVERY	Randomised Evaluation of SARS-COV-2 Therapy
RT-PCR	Reverse-transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WBC	White blood cells

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104105.

References

[1] W. Zhou, Y. Liu, D. Tian, et al., Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia, Signal Transduct. Targeted Ther. 5 (2020) 18.
[2] H. Li, C. Chen, F. Hu, et al., Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis, Leukemia 34 (2020) 1503–1511.
[3] K.K. Gangopadhyay, J. Mukherjee, B. Sinha, S. Ghosal, Role of corticosteroids in the management of critically ill patients with coronavirus disease 2019 (COVID-19): a meta-analysis, medRxiv (2020), https://doi.org/10.1101/2020.04.17.20069773, 04.17.20069773.
[4] Z. Yang, J. Liu, Y. Zhou, X. Zhao, Q. Zhao, J. Liu, The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis, J. Infect. 81 (2020) e13–e20.
[5] The RECOVERY Collaborative Group, Dexamethasone in hospitalized patients with Covid-19, N. Engl. J. Med. 384 (2021) 693–704.
[6] K.P. Steinberg, Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome, N. Engl. J. Med. 354 (2006) 1671–1684.
[7] S. Sarkar, P. Khanna, K.D. Soni, Are the steroids a blanket solution for COVID-19? A systematic review and meta-analysis, J. Med. Virol. 93 (2021) 1538–1547.
[8] N. Lee, K.C. Allen Chan, D.S. Hui, et al., Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients, J. Clin. Virol. 31 (2004) 304–309.
[9] R. Fadel, A.R. Morrison, A. Vahia, et al., Henry Ford COVID-19 Management Task Force, Early short course corticosteroids in hospitalized patients with COVID-19, Clin. Infect. Dis. 71 (2020) 2114–2120.
[10] U. Boregowda, A. Perisetti, A. Nanjappa, M. Gajendran, G. Kutti Sridharan, H. Goyal, Addition of tocilizumab to the standard of care reduces mortality in severe COVID-19: a systematic review and meta-analysis, Front. Med. 7 (2020), 586221.
[11] M. Al-Jarallah, R. Rajan, A.A. Saber, et al., In-hospital mortality in SARS-CoV-2 stratified by hemoglobin levels: a retrospective study, eJHaem (2021), https://doi.org/10.1002/jha2.195.
[12] M. Al-Jarallah, R. Rajan, AAl Saber, et al., In-hospital Mortality in SARS-CoV-2 stratified by serum 25-Hydroxy-Vitamin D levels: a Retrospective Study, J. Med. Virol. 93 (2021) 5880–5885.
[13] M. Alroomi, R. Rajan, A.A. Omar, et al., Ferritin level: a predictor of severity and mortality in hospitalized COVID-19 patients, Immun Inflamm Dis (2021) 1–8, https://doi.org/10.1002/iid3.517.
[14] M. Al Saleh, N. Alotaibi, K. Schrapp, et al., Risk factors for mortality in patients with COVID-19: the Kuwait experience, Med. Princ. Pract. 31 (2022) 180–186.
[15] M. Alroomi, R. Rajan, A. Alsaber, et al., In-hospital mortality in SARS-CoV-2 stratified by gamma-glutamyl transferase levels, J. Clin. Lab. Anal. 36 (2022), e24291.
[16] G. Mathew, R. Agha, for the STROCSS Group, Strocss 2021: strengthening the Reporting of cohort, cross-sectional and case-control studies in Surgery, Int. J. Surg. 96 (2021), 106165.
[17] M. Alroomi, N. Alotaibi, R. Rajan, Browse the registry - research registry [Internet], Res. Registry (2022) [cited 16 June 2022]. Available from: https://www.researchregistry.com/browse-the-registry#home/registrationdetails/62ab5dd554853e001e097baf/.
[18] T. Laine, E.M. Reyes, Tutorial: survival estimation for Cox regression models with time-varying coefficients using SAS and R, J. Stat. Software 61 (2014) 1–23.
[19] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, J.A.C. Sterne, S. Murthy, et al., Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis, JAMA 324 (2020) 1330–1341.
[20] S. Lu, Q. Zhou, L. Huang, et al., Effectiveness and safety of glucocorticoids to treat COVID-19: a rapid review and meta-analysis, Ann. Transl. Med. 8 (2020) 627.
[21] X. Li, S. Xu, M. Yu, et al., Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan, J. Allergy Clin. Immunol. 146 (2020) 110–118.
[22] N.A. Resk, M.A. Ibrahim, Effects of methyl prednisolone in early ARDS, Egypt. J. Chest Dis. Tuberc. 62 (2013) 167–172.
[23] E.J. Cano, X.F. Fuentes, C.C. Campioli, et al., Impact of corticosteroids in COVID-19 outcomes: systematic review and meta-analysis, Chest 159 (2021) 1019–1040.
[24] A. Bahl, S. Johnson, N.W. Chen, Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients, Intern Emerg Med 5 (2021) 1–11.
[25] F. Fang, Y. Zhang, J. Tang, et al., Association of corticosteroid treatment with outcomes in adult patients with sepsis: a systematic review and meta-analysis, JAMA Intern. Med. 179 (2019) 213.
[26] S. Weber-Carstens, M. Deja, S. Bercker, et al., Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients, Intensive Care Med. 33 (2007) 730–733.
[27] D.R. Giacobbe, D. Battaglini, L. Ball, et al., Bloodstream infections in critically ill patients with COVID-19, Eur. J. Clin. Invest. 50 (2020), e13319.

[28] J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell, Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review, JAMA 323 (2020) 1824–1836.
[29] J. Villar, C. Ferrando, D. Martínez, et al., Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial, Lancet Respir. Med. 8 (2020) 267–276.
[30] L. Zha, S. Li, L. Pan, et al., Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19), Med. J. Aust. 212 (2020) 416–420.
[31] T. Sahilu, T. Sheleme, T. Melaku, Severity and mortality associated with steroid use among patients with COVID-19: a systematic review and meta-analysis, Interdiscip Perspect Infect Dis (2021), 6650469, 2021.
[32] World Health Organization, WHO welcomes preliminary results about dexamethasone use in treating critically ill COVID-19 patients. https://www.who.int/news-room/detail/16-06-2020-who-welcomes-preliminary-results-about-dexamethasoneuse-in-treating-critically-ill-covid-19-patients, June 2020.
[33] World Health Organization, in: Clinical Management of Severe Acute Respiratory Infection when COVID-19 Is Suspected, World Health Organization, Geneva, 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acuteres piratory-infection-when-novel-coronavirus-(ncov)-infection-issuspected.
[34] A. Dagens, L. Sigfrid, E. Cai, et al., Scope, quality, and inclusivity of clinical guidelines produced early in the covid-19 pandemic: rapid review, BMJ 369 (2020) m1936.
[35] R. Siemieniuk, B. Rochwerg, T. Agoritsas, et al., A living WHO guideline on drugs for Covid-19, BMJ 370 (2020) m3379.
[36] C. Whitty, Dexamethasone in the treatment of COVID-19: implementation and management of supply for treatment in hospitals, in: London: Medicines and Healthcare Products Regulatory Agency, June 16, 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103054.
[37] COVID-19 Treatment Guidelines: Corticosteroids, National Institutes of Health, Bethesda, MD, 2020. https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/corticosteroids/.