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Dexamethasone chronotherapy of COVID-19 patients admitted to intensive care unit: an exploratory study

Mohammad Abusamak^{1,2} , Ali Ait Hssain^{3,4,5} , Venkateswara Rao Chinta⁶, Haider Al-Waeli² , Hadi M. Yassine⁷ and Faleh Tamimi^{1,8,9*}

Abstract

Background Dexamethasone has been demonstrated to be a potential treatment approach preventing COVID-19 related fatalities by managing the cytokine release storm (CRS). The expression of the inflammatory mediators involved in the CRS is regulated by the circadian biology of the immune response and it peaks during the evening. Accordingly, it has been hypothesized that the administration of anti-inflammatory medications in the evening could help better manage the CRS. Therefore, we investigated the association between dexamethasone administration time and COVID-19 mortality.

Methods A retrospective cohort study was conducted using electronic health records of COVID-19 patients hospitalized in the State of Qatar between March 2020 and April 2021. The exposure group received dexamethasone between 16:00 h and 04:00 h, while the control group received dexamethasone between 04:00 h and 16:00 h.

Results From the 875 COVID-19 patients included in the study, 161 received dexamethasone treatments between 16:00 h and 04:00 h while 714 received it between 04:00 h and 16:00 h. After adjusting for confounding variables, dexamethasone given between 16:00 h and 04:00 h was associated with lower odds of COVID-19 mortality (OR: 0.22, CI 95%: 0.06, 0.84).

Conclusion Dexamethasone administration tailored to the circadian rhythm was associated with lower odds of mortality in hospitalized COVID-19 patients.

Keywords COVID-19, Chronotherapy, Dexamethasone, Inflammation, ICU, Mortality

*Correspondence:

Faleh Tamimi

fmarino@qu.edu.qa; faleh.tamimimarino@mcgill.ca

¹Faculty of Dental Medicine and Oral Health Sciences, McGill University, Montreal, QC, Canada

²Faculty of Dentistry, Dalhousie University, Halifax, NS, Canada

³Medical Intensive Care Unit, Hamad Medical Corporation, Doha, Qatar

⁴Department of medicine, Weill Cornell Medicine-Qatar, Doha, Qatar

⁵College of Health and Life Sciences, Hamad Bin Khalifa University (HBKU), Doha, Qatar

⁶Department of Business Intelligence, Hamad Medical Corporation, Doha, Qatar

⁷Biomedical Research Center, QU Health, Qatar University, Doha, Qatar

⁸College of Dental Medicine, Qatar University, Doha, Qatar

⁹School of Dentistry, University of Jordan, Amman, Jordan



Introduction

The widely spread viral infection caused by the SARS-CoV-2 virus has led to the COVID-19 global pandemic that started in late 2019 [1]. This viral infection can cause an Acute Respiratory Distress Syndrome (ARDS), which can lead to respiratory failure and death [2]. The so-called cytokine release storm (CRS), which causes COVID-19-induced ARDS, is a two-edged weapon, that is, CRS is a physiological inflammatory defense reaction that accelerates viral clearance, but in severe cases, the inflammatory reaction is exaggerated causing pulmonary destruction eventually terminating in ARDS and death [3]. In infected individuals, SARS-CoV-2 virus triggers immune reactions leading to up-regulated inflammatory mediators such as Interleukin (IL)-1, IL-6, IL-10, and Tumor Necrosis Factor (TNF)- α [1, 4, 5]. Thus, prescribing immunosuppressive agents to manage the hyperinflammatory state associated with COVID-19 infection is a potential therapeutic approach [6, 7].

In this sense, there has been an increased interest in the use of corticosteroids (i.e., dexamethasone) for managing COVID-19-induced ARDS, mainly, due to their potent anti-inflammatory effect and potential ability to modulate inflammation-mediated lung injury [6, 8–10]. This interest has grown substantially especially after the release of the results from the RECOVERY trial on hospitalised COVID-19 patients, which demonstrated that

low-dose dexamethasone (6 mg) reduced the death rate by one fifth and one third compared to patients receiving oxygen only, and mechanical ventilation, respectively [7, 11]. However, the therapeutic role of corticosteroids in managing COVID-19-induced ARDS remains controversial [12–14]. Corticosteroids inhibit several key detrimental inflammatory cytokines relevant to ARDS including, IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, TNF- α , IL-10, IL-13, Granulocyte–Macrophage Colony-Stimulating-Factor (GM-CSF), Monocyte Chemoattractant Protein (MCP)-1 and Interferon gamma-induced protein (IP)-10 [15–18]. However, they can also disrupt the anti-viral response by stimulating T-cells apoptosis, causing B-cells depletion, and inhibiting neutrophils activation causing a higher risk of mortality and secondary infections [15, 19, 20]. Accordingly, even though corticosteroids could be beneficial in severe COVID-19 cases, they still could have a detrimental effect on mild cases by inhibiting the body's ability to fight the viral infection. Thus, the ideal therapy should be able to inhibit the detrimental cytokines while preserving the ability of the body to fight the infection. More selective anti-inflammatory medications such as interleukin inhibitors (IL-1 & IL-6) [21, 22], interferons [23], and kinase inhibitors [24] have been investigated for managing the CRS. However, thus far, these medications have shown limited benefits in treating COVID-19 patients [25], and their high costs prevents them from being used at a large scale specially in developing countries. Hence, a better anti-inflammatory treatment modality is needed.

In all vertebrates, the sleep-awake cycle of the circadian rhythm is a vital behavioural state, and it is essential for mental and physical health [26, 27]. The circadian clock is an essential modulator for daily physiological processes including our immune system; both the innate and adaptive immune systems activity, and subsequently the inflammatory immune responses, are vigorously orchestrated by our circadian rhythms [28]. Due to the regulatory nature of peripheral circadian clocks in our immune system, the diurnal variation of antiviral activity and inflammatory cytokines, and the time of viral infection affect the survival of infected subjects [29, 30]. In fact, disturbed biological rhythms nourishes a severe form of viral infections accelerating virus spreading and replication [29].

The cytokines associated with ARDS exhibit a circadian rhythm in which they peak at different times of the day (~ 24h) (Table 1). Figure 1 maps the peak expression time of both the detrimental inflammatory cytokines and anti-viral immune cells activity. For instance, TNF- α peaks twice in the morning and once in the afternoon, IL-8 peaks later in the morning and again at night, MCP-1 and IL-1 peak at bedtime and at 2 AM, respectively, while GM-CSF peaks in the afternoon and at night.

Table 1 Inflammatory cytokines and immune cells involved in COVID-19-induced ARDS

Inflammatory mediators	Role in viral infections [13–16]	Effect of corticosteroids [13–16]	Peak expression
Cytokines			
IL-6	Involved in CRS	Inhibition	05:00 h & 19:00 h [34]
TNF- α	"	"	07:30 h & 12:00 h-13:30 h [35–37]
IL-1	"	"	Bedtime [38]
IL-8	"	"	10:00 h & 21:00 h [37]
GM-CSF	"	"	13:30 h & 19:30 h-23:30 h [35, 37]
MCP-1	"	"	02:00 h [37]
IL-10	Involved in both CRS and anti-viral response	Inhibition	07:30 h & 19:30 h [35]
Immune cells			
CD4+ & CD8+	Involved in anti-viral response	T-cell apoptosis	02:00 h [33]
Effector CD8+	"	"	14:00 h [33]
B-cells	"	B-cell depletion	02:00 h-03:00 h [39]

Abbreviations: IL Interleukin, TNF Tumour Necrosis Factor, GM-CSF Granulocyte–Macrophage Colony-Stimulating-Factor, MCP Monocyte Chemoattractant Protein

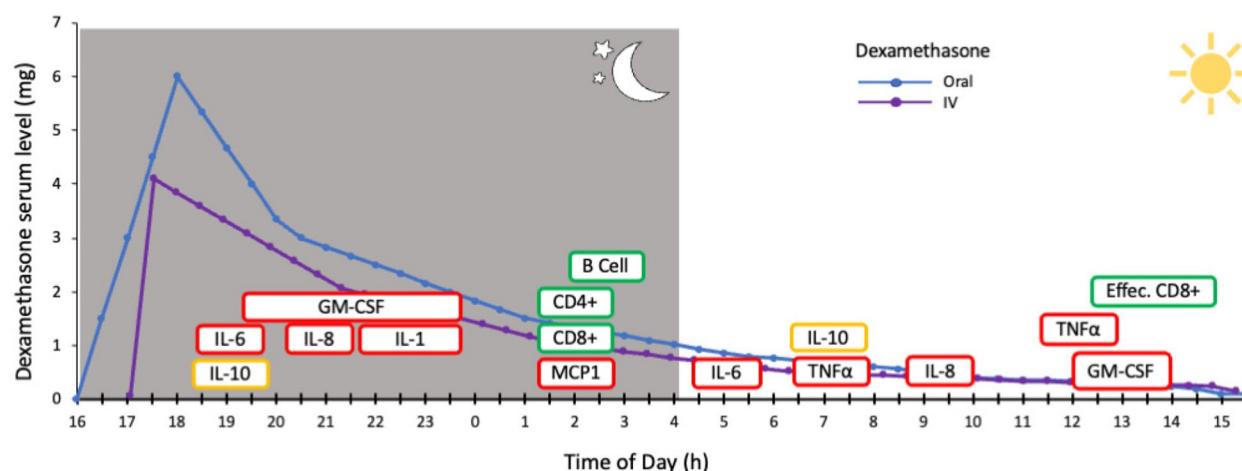


Fig. 1 Diagram illustrating the peaks of maximum activity of both determinantal (Red), and beneficial (Green) inflammatory mediators involved in the CRS during the 24h day cycle (24h). The diagram also shows the hypothetical serum levels IV (purple line) and Oral (blue line) Dexamethasone upon administration at our hypothetical time window optimized for managing the CRS. Abbreviations: IL: Interleukin, TNF: Tumour Necrosis Factor, GM-CSF: Granulocyte–Macrophage Colony-Stimulating-Factor, MCP: Monocyte Chemoattractant Protein

The anti-viral response also exhibits a diurnal rhythm in which the highest cytotoxic activity of CD4 and CD8 T cells against viral antigens is during nighttime (Table 1) [31–33]. So, it is pertinent to investigate the best dosing time for preventing the CRS, whilst minimising the risk of secondary infections and prolonged viral shedding.

The circadian clock regulates the expression of several therapeutic targets and proteins that play a key role in drug metabolism, thus influencing the efficacy and pharmacokinetics [40]. In fact, it is estimated that more than 80% of FDA-approved drugs targets might show a diurnal variation of their mRNA expression levels and corresponding functions [41, 42]. Thus, chronotherapy, the treatment of disease by administering drugs at the time of the day that is in harmony with the body's circadian rhythms, has emerged as a promising field that can improve the therapeutic efficacy and decrease the side effects of many treatments. Chronotherapy has also been shown to be very effective resetting and re-synchronizing disturbed circadian rhythms, in conditions associated with disturbed clocks [43, 44]. The sleep cycles and the circadian rhythm are significantly disrupted in critically ill patients, possibly due to sleep disturbing factors such as sedation and mechanical ventilation [26, 45], and drug chronotherapy could actually help restore the circadian clock back to normal in such conditions [46].

A recent animal study led by Dr Tamimi has shown that the impact of anti-inflammatory drugs on cellular activity and cytokine levels in injured tissues depends on the dosing time [47]. In addition, this study also demonstrated NSAID chronotherapy has the potential to reset the clock gene *Per2* [47]. Based on these observations described above a team of researchers from Canada, the USA and Qatar, led by Dr Tamimi has hypothesized that

by targeting the peak expressions of detrimental inflammatory mediators in the CRS, anti-inflammatory drugs could effectively manage COVID-19 induced ARDS [48].

Dexamethasone is a potent glucocorticoid receptor agonist that could be prescribed both orally and intravenously (IV) [13]. In adults, oral administration of dexamethasone takes 1 to 2 h to peak in the blood serum and requires around 4 h to reach its half-life [49]. On the other hand, IV administration of dexamethasone takes 5 to 10 min to reach the maximum plasma concentration level and then requires 1 to 5 h to reach its half-life [50–53]. Since anti-viral immune cells peak during nighttime and most CRS pro-inflammatory cytokines peak in the afternoon, thus prescribing dexamethasone at night should be avoided. However, targeting the peak expression of detrimental cytokines in the afternoon is desired. More specifically, based on the peak expressions of inflammatory cytokines and the peak time of Dexamethasone serum levels, we hypothesize that a single dose of dexamethasone administered between 4–5 pm would result in improved outcomes on the treatment of COVID-19 patients. This administration regimen, tailored to the circadian biology of both the medication and immune response, might effectively manage COVID-19-induced ARDS, while attenuating the risk of prolonged viral clearance and secondary bacterial infections. Our research question is as follows: Among hospitalized COVID-19 patients, to what extent is dexamethasone chronotherapy (explicit re-scheduling of medication administration) associated with reduced COVID-19 mortality rates and improved clinical outcomes such as reduced length of hospital stay (LOS). Therefore, we conducted a retrospective cohort study to investigate the

association between dexamethasone administration time and COVID-19 mortality.

Method

Study population

Hamad Medical Corporation's (HMC) hospitalized patients, diagnosed with COVID-19, were selected from the national electronic health records in the state of Qatar. All patients with confirmed COVID-19 diagnosis and have been hospitalized from March 1st, 2020, to April 20th, 2021, were included if they meet our inclusion criteria. Our inclusion criteria were: (i) Adults aged 18 y or older (ii) Discharged or deceased after admission to intensive care unit (ICU) due to COVID-19 (iii) Dexamethasone (IV) was prescribed for treatment. On the other hand, patients who were prescribed dexamethasone combined with either methylprednisolone, tocilizumab, or both were excluded. Patients that were admitted to the ICU before COVID-19 diagnosis were also excluded.

This study was approved by the Institutional Review Board of HMC (RP MRC-01–20–145) with a waiver of informed consent under the pandemic response framework, and all retrieved medical records were de-identified before extraction. Also, all methods used in this study were conducted by the relevant guidelines and regulations (such as the Declaration of Helsinki).

Study design

This retrospective cohort study of COVID-19 mortality evaluating dosing time of dexamethasone as exposure. The exposure (Chronotherapy) group was defined as the patients who received dexamethasone (IV) between 16:00 h and 04:00 h, while the control group was defined as patients given dexamethasone (IV) between 04:00 h and 16:00 h. Patients who received $\geq 75\%$ of their dexamethasone doses between 16:00 h and 04:00 h were included in the exposure (Chronotherapy) group. On the other hand, patients who received $\geq 75\%$ of their doses between 04:00 h and 16:00 h were included in the control group. Consequently, patients (1) with equal number of doses between both groups, or (2) has been admitted to ICU more than once due to COVID-19 were excluded. The duration of dexamethasone administration in days was calculated as the difference between the date of first dose after admission date and the last dose upon discharge/death.

The primary outcome of this study was COVID-19 mortality (Death/Discharge), and the secondary outcomes were recovery duration through the length of stay in the hospital (Admission Date– Outcome (Discharge or Death) Date) and need for invasive mechanical ventilation. Finally, as an explanatory outcome, we assessed the management of hyperinflammation state caused by the viral infection which was reflected in laboratory

biomarkers measured (Lymphocytes, D-Dimer, RBS, LDH, Ferritin, and CRP) after ICU admission. Three categories of inflammation degree risk (low, intermediate, and high risk) were determined by calculating the terciles of CRP, D-Dimer, LDH and Ferritin at the time of admission [54].

Further, data on demographics (Age and Sex) and other clinical risk factors that influence COVID-19 mortality were extracted and categorized as follows:

1. Body Mass Index (BMI kg/m^2), categorized as underweight/adequate ($\text{BMI} \leq 25$) and overweight/obese ($\text{BMI} > 25$)
2. Smoking status categorized as never and present/former.
3. Comorbidities (Present/Absent) namely, Diabetes, Hypertension, Myocardial infarction, Angina, Chronic lung, liver, and kidney conditions, Dialysis, Leukemia, Lymphoma, and other cancers. This was categorized as Healthy (no comorbidity), One comorbidity, and Two or more comorbidity.
4. Medications namely, Hydrocortisone, Hydroxychloroquine, Azithromycin, Lopinavir Ritonavir, and Ribavirin. This was categorized as Yes (present) and No (absent).
5. COVID-19 waves were categorized into Wild-type (Before Jan 17th, 2021), Alpha (between Jan 18th, 2021, to March 10th, 2021), and Beta (March 11th, 2021, to June 2021)

Data analysis

Associations between dexamethasone administration time and COVID-19 mortality and need for ventilation were reported as odd ratios (OR) and 95% confidence intervals (95% CI) was analyzed using logistic regression models adjusted for demographic and clinical variables such as age, sex, comorbidity, BMI, Dexamethasone dose and Hydroxychloroquine. Continuous variables were compared using Kruskal–Wallis Rank Sum Test, while categorical variables were compared using Pearson's Chi-squared test. Finally, Laboratory biomarkers were compared between study groups using Kruskal–Wallis Rank Sum Test. All statistical analyses were conducted using the statistical program R version 4.0.2 (R Foundation).

Results

The medical records of 3359 patients hospitalized due to COVID-19 were obtained for our study. Among these, 14 patients were excluded due to their age (< 18 y), 21 patients were excluded for being admitted more than once, and 116 patients were excluded for having equal number of doses received in both groups. Further, 2333 patients were excluded because they were treated with

methylprednisolone, tocilizumab, or both, and only 875 were included for analysis (Fig. 2).

From these patients, 272 were admitted to the ICU without prior hospitalization, while 603 were hospitalized before ICU admission (Supplementary Table 1). Overall, 70.5% of the study population were males, 81.1% were overweight/obese, 10.0% were smokers, and 68.5% presented with one or more comorbidity (Supplementary Table 2). Among the patients included, 161 took dexamethasone between 16:00 h and 04:00 h (Chronotherapy group), while 714 were given dexamethasone between 04:00 h and 16:00 h (Control group). Table 2 presents demographical and clinical variables distribution among our study groups. Dexamethasone dose was significantly different between groups ($p < 0.05$), however the remaining population study characteristics seemed to be equally distributed ($p > 0.05$).

The association between administration time of dexamethasone and COVID-19 mortality is shown in Table 3. Dexamethasone administration between 16:00 h and 04:00 h (Chronotherapy group) was associated with lower odds of COVID-19 mortality (OR = 0.44; CI 95%: 0.20, 0.98) than Dexamethasone administration between 04:00 h and 16:00 h. This association remained significant after adjusting for confounding variables such as age, sex, comorbidity, BMI, dexamethasone dose, inflammation degree risk categories and wave type (OR: 0.22, CI 95%:

0.06, 0.84). Only 20.6% of the study population needed invasive mechanical ventilation and patients receiving dexamethasone between 16:00 h and 4:00 h were also less likely to need invasive mechanical ventilation. In addition, the median of hospital length of stay was 15 days in both groups with no significant difference between them ($p > 0.05$).

The association between dexamethasone administration time and the last measured laboratory biomarkers after ICU admission are shown in Table 4. Upon ICU admission, blood levels of CRP, D-Dimer, LDH, Lymphocytes and Ferritin were significantly lower in the chronotherapy group than in the control group. Three days after ICU admission, both D-Dimer and Lymphocytes serum levels remained significantly lower in the chronotherapy. Further, seven days after ICU admission D-Dimer, Lymphocytes and LDH were significantly lower in the chronotherapy. Subgroup analysis of patients admitted directly to the ICU without prior hospitalization also showed that both D-Dimer and LDH levels were significantly lower in the chronotherapy group upon ICU admission, while D-Dimer remained significantly lower in the chronotherapy group after ICU admission (Supplementary Table 3). Inflammation degree risk categories were as follows: high risk (62.7% vs 75.5%), intermediate risk (32.7% vs 21.6%) and low risk (4.7% vs 2.9%) for the chronotherapy and control groups, respectively.

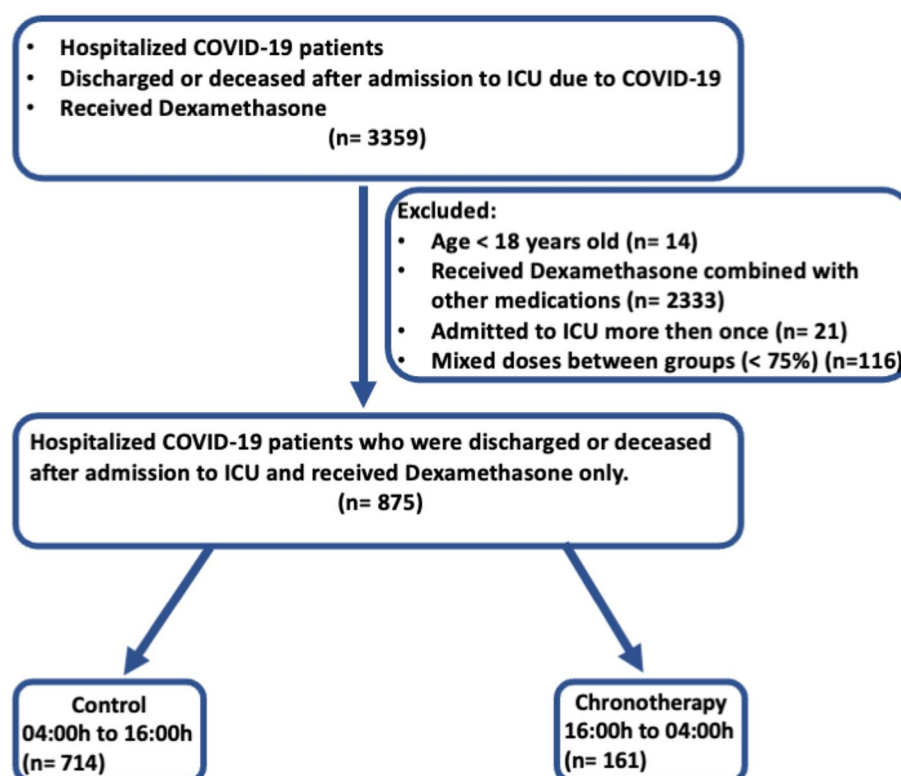


Fig. 2 Study flowchart. (Abbreviations: ICU: Intensive Care Unit.)

Table 2 Demographics and clinical variables stratified by dexamethasone administration time

Variables	Chronotherapy (16:00–4:00) (n = 161)	Control (4:00–16:00) (n = 714)	P
Sex (%)			0.441 ^a
Female	52 (32.3)	206 (28.9)	
Male	109 (67.7)	508 (71.1)	
Age (median [IQR])	48.00 [40.00, 58.00]	48.00 [39.25, 58.00]	0.835 ^b
Nationality (%)			0.156 ^a
Bangladeshi	9 (5.6)	62 (8.7)	
Egyptian	12 (7.5)	43 (6.0)	
Filipino	30 (18.6)	117 (16.4)	
Indian	38 (23.6)	141 (19.7)	
Iranian	2 (1.2)	17 (2.4)	
Jordanian	1 (0.6)	20 (2.8)	
Nepalese	11 (6.8)	40 (5.6)	
Pakistani	20 (12.4)	48 (6.7)	
Palestinian	4 (2.5)	24 (3.4)	
Qatari	8 (5.0)	69 (9.7)	
Sudanese	6 (3.7)	25 (3.5)	
Syrian	5 (3.1)	26 (3.6)	
Other Nationalities	15 (9.3)	82 (11.5)	
BMI (%)			0.621 ^a
Underweight/Adequate	25 (15.5)	121 (16.9)	
Overweight/Obese	131 (81.4)	579 (81.1)	
Missing	5 (3.1)	14 (2.0)	
Smoking (%)			0.137 ^a
Never	133 (82.6)	544 (76.2)	
Present/Former	15 (9.3)	73 (10.2)	
Missing	13 (8.1)	97 (13.6)	
Comorbidity (%)			0.900 ^a
Healthy	46 (28.6)	194 (27.2)	
One comorbidity	49 (30.4)	214 (30.0)	
Two or more comorbidities	66 (41.0)	306 (42.9)	
COVID-19 Vaccine Before ICU Admission			
One Dose Only (%)			0.318 ^a
No	112 (69.6)	458 (64.1)	
Yes	8 (5.0)	31 (4.3)	
Two Doses (%)			0.473 ^a
No	108 (67.1)	450 (63.0)	
Yes	0 (0.0)	3 (0.4)	
COVID-19			
Wave Type (% between groups)			0.054 ^a
Wild-type Wave (Before Jan 17th, 2021)	39 (24.2)	124 (17.4)	
Alpha Wave (Jan 18th, 2021, to March 10th, 2021)	48 (29.8)	194 (27.2)	
Beta Wave (March 11th, 2021, to June 2021)	74 (46.0)	396 (55.5)	
Hospital Length of Stay in days (median [IQR])	15.00 [11.00, 18.00]	15.00 [11.00, 21.00]	0.223 ^b
Dexamethasone			
On medication– days (median [IQR])	13.00 [10.00, 16.00]	13.00 [10.00, 19.00]	0.241 ^b
Dose– mg (median [IQR])	7.90 (0.81)	7.71 (0.76)	0.006^b
Other Medications Taken			
Hydrocortisone (%)	12 (7.5)	64 (9.0)	0.646 ^a
Hydroxychloroquine (%)	48 (29.8)	161 (22.5)	0.064 ^a
Azithromycin (%)	130 (80.7)	584 (81.8)	0.844 ^a

Table 2 (continued)

Variables	Chronotherapy (16:00–4:00) (n = 161)	Control (4:00–16:00) (n = 714)	P
Lopinavir ritonavir (%)	65 (40.4)	243 (34.0)	0.153 ^a
Ribavirin (%)	19 (11.8)	70 (9.8)	0.540 ^a

Abbreviations: BMI Body Mass Index, ICU Intensive Care Unit

^aPearson's Chi-squared test^bKruskal-Wallis Rank Sum Test**Table 3** Associations between dexamethasone administration time and COVID-19 mortality

Dexametha- sone Adminis- tration Time	Outcome		OR (CI 95%)	Adjusted OR (CI 95%) ^a
	Death	Discharge		
Control	70	644	1	1
Chronotherapy	8	153	0.44 (0.20, 0.98); <i>p</i> < 0.05	0.22(0.06, 0.84); <i>p</i> < 0.05
	Ventilated	Not Ventilated		
Control	176	538	1	1
Chronotherapy	13	148	0.22 (0.11–0.43); <i>p</i> < 0.05	0.20 (0.10, 0.40); <i>p</i> < 0.05

Vaccinated patients were excluded from this analysis (n = 39)

Abbreviations: OR Odds Ratio, CI Confidence Interval

^aAdjusted for age, sex, comorbidity, BMI, Dexamethasone dose, inflammation degree risk categories and Wave Type

Discussion

This study demonstrated that tailoring the schedule of Dexamethasone treatment (Chronotherapy) according to the circadian rhythm of the immune system, significantly reduced COVID-19 death in hospitalized patients. That is, dexamethasone administration between 16:00 h and 04:00 h showed a significant reduction in the odds of mortality by 44% and a reduction in the blood levels of inflammatory cytokines. We also observed that risk factors such as age, body mass index, and the presence of two or more comorbidities were associated with COVID-19 mortality which is in accordance with previous studies investigating COVID-19 risk factors [55–58].

In this study we observed that once the dexamethasone treatment was started in a given hour most patients would keep receiving the treatment at the same time in order to maintain the therapeutic effect of the drug.

Table 4 Laboratory data upon and after ICU admission stratified by dexamethasone administration time

Laboratory parameters	Chronotherapy (n = 161) (16:00–4:00)		Control (n = 714) (4:00–16:00)		P ^a	SMD ^b
	n	median [IQR]	n	median [IQR]		
Upon ICU admission						
CRP (mg/L)	147	59.10 [31.00, 107.00]	673	73.00 [33.40, 133.00]	0.020	0.274
D-Dimer (mg/L)	141	0.54 [0.37, 1.00]	650	0.74 [0.47, 1.44]	< 0.001	0.164
RBS (mg/dL)	5	5.10 [4.60, 6.20]	24	7.50 [5.70, 9.00]	0.106	0.911
LDH (U/L)	134	367.50 [276.00, 480.75]	583	408.00 [305.00, 536.00]	0.022	0.214
Lymphocyte (10 ³ /μL)	158	0.70 [0.50, 1.00]	705	0.80 [0.60, 1.10]	0.012	0.057
Ferritin (μg/L)	152	606.00 [288.75, 1263.25]	675	758.00 [398.00, 1412.50]	0.033	0.143
Three days after ICU Admission						
CRP (mg/L)	101	18.50 [8.50, 46.00]	557	21.00 [9.00, 39.60]	0.719	< 0.001
D-Dimer (mg/L)	120	0.82 [0.46, 1.57]	580	0.99 [0.56, 2.31]	0.019	0.172
RBS (mg/dL)	3	5.10 [4.85, 6.75]	13	7.10 [4.80, 8.50]	0.590	0.578
LDH (U/L)	87	282.00 [192.00, 420.00]	447	321.00 [196.00, 427.50]	0.213	0.067
Lymphocyte (10 ³ /μL)	137	0.90 [0.60, 1.40]	654	1.20 [0.80, 1.70]	< 0.001	0.027
Ferritin (μg/L)	126	523.00 [144.25, 1098.50]	597	483.00 [154.00, 937.00]	0.865	0.091
Seven days after ICU Admission						
CRP (mg/L)	48	15.00 [6.00, 55.25]	313	16.80 [6.00, 47.10]	0.783	0.068
D-Dimer (mg/L)	77	0.76 [0.45, 1.60]	383	1.33 [0.66, 2.68]	0.001	0.333
RBS (mg/dL)	2	4.85 [4.72, 4.97]	10	7.50 [4.95, 8.28]	0.237	1.177
LDH (U/L)	50	238.50 [78.75, 331.00]	266	304.00 [223.25, 407.75]	0.013	0.219
Lymphocyte (10 ³ /μL)	81	1.30 [0.80, 2.00]	443	1.50 [1.00, 2.10]	0.024	0.050
Ferritin (μg/L)	75	415.00 [135.00, 763.50]	381	451.00 [127.00, 915.00]	0.563	0.195

^aKruskal-Wallis Rank Sum Test^bStandardized Mean Differences

However, the time of the day in which patients received dexamethasone varied, and this was probably due to variability in the time of the day in which the treatment was started. These variations seemed to be random because there were no significant differences between patients receiving the drug during the day or during the night in terms of comorbidities or demographic variables. However, despite this randomness in the timing in which the patients started treatment, the odds of death associated with the patients receiving the treatment at night was significantly lower than for those receiving it during the day. Moreover, this association remain significant after adjusting for confounding factors such as patients' comorbidities and demographic characteristics.

Dexamethasone is already known to have beneficial effects on COVID-19 patients; however, our findings would suggest that these benefits could be further improved by optimizing the time of the day in which the drug is given. Although future interventional studies would be needed to confirm this possibility; our study is observational in nature thus it cannot confirm causality. Randomized controlled trials would be needed to confirm our findings. Moreover, as per the protocol of the health care system in Qatar at the time of the study, dexamethasone was prescribed to all hospitalized COVID-19, even if they were not admitted to the ICU. This study, however, only included patients who were admitted to the ICU and received dexamethasone whom by default were probably at higher risk of dying, thus the effect we observed could be less pronounced in less sick patients.

The effect of dexamethasone chronotherapy on COVID-19 mortality that we observed could be explained by the circadian behaviour of the inflammatory cytokines up-regulated by COVID-19. These key detrimental cytokines which have been associated with COVID mortality (e.g., D-Dimer IL-1, IL-6, IL-8, and TNF- α) are overly expressed in the afternoon. Therefore, it could be speculated that dexamethasone administration targeting the circadian peak expression of these cytokines selectively manage the hyperinflammatory state without disrupting the body's immune response and ability to fight the virus. Indeed, in our study we observed that dexamethasone administration in the night (16:00–4:00) resulted in lower blood levels of these inflammatory biomarkers.

Ventilated patients are known to have disrupted circadian rhythm due to the sedation [26, 45]. For this reason, if our hypothesis was correct, we would expect a strong effect of chronotherapy in these patients. Indeed, subgroup analyses limited only to the ventilated patients ($n=189$) showed lower mortality rate fewer days on medications and shorter stay in the hospital in the chronotherapy group than in the control group, although the sample of this subgroups was too small to assess significance (Supplementary Table 4). In addition, among

ventilated patients, the blood levels of Lymphocyte upon ICU admission and D-Dimer after seven days of ICU admission were significantly lower in the chronotherapy group than in the control group (Supplementary Table 5).

This study has several limitations. First, despite that retrospective design is inherently limited by potential confounding and missing variables, we attempted to mitigate these via adjusted analyses. Second, even though our exposure was time sensitive, the time of the day in which dexamethasone was administered varied across patients and within the same patient. Interpatient variability was beneficial for our research because it allowed us to assess the effect of different administration times on disease outcome, however intra-patient variability could have compromised our ability to test our hypothesis. With that said, we only included patients who received Dexamethasone in a somehow regular timely manner, throughout their stay in the ICU. Although future clinical trials with strict control on administration time would be needed to better address this issue. Further, the period in which we extracted our data witnessed major changes in treatment protocols and modalities in managing ARDS, whether in medications used or Dexamethasone dose specifically. However, after adjusting for Dexamethasone dose, the reduction in COVID-19 mortality remained significant. Another limitation of this study was the confounding by indication. We had no control on the reason why some patients received Dexamethasone at different times of the day. One possible reason for this could have been the time of admission. Indeed, we observed that a higher probability for a patient to be in the chronotherapy group was found when they are admitted to ICU at 15:00 h while the lowest was at 04:00 h (Supplementary Fig. 1). In order to assess the possible bias created by the time of admission we investigated the possible associations between the risk of death and the time of admission, however, the data revealed that mortality was not influenced by admission time (Supplementary Fig. 2). One more limitation is the baseline inflammatory markers could not be recorded for included patients. Because the dates of lab results are not available, so admissions timeline regarding these lab results could not be established. Therefore, the disease severity of patients at admission could not be assessed. Also, inflammatory mediators' levels upon admission to the ICU were significantly lower in the chronotherapy group, and this difference decreased over time. As per hospital protocol, treatment with dexamethasone was initiated immediately even before ICU admission or blood tests were taken. In other words, inflammatory mediators upon ICU admission does not represent baseline levels. However, both groups were relatively similar in terms of demographics, medical history and vaccination status and we adjusted for inflammatory biomarkers levels in our analysis.

Further, this retrospective study was conducted during the early stages of the COVID-19 pandemic, prior to widespread vaccination and the emergence of newer variants of the disease. Therefore, these data should be interpreted with caution when applying it to later stages of the pandemic or different variants of COVID-19. Nonetheless, the observed association between dexamethasone dosing time and mortality could be relevant to other hyperinflammatory conditions or future viral outbreaks. Finally, although validated indices such as the Charlson Comorbidity Index and WHO COVID-19 severity classification scale offer standardized risk scoring, the retrospective nature and data limitations precluded its use in our cohort. However, the inflammatory biomarkers in the ventilated subset were very similar between groups upon ICU admission. Further, after adjusting for several inflammatory biomarkers, the OR remained significant. These findings support our hypothesis that dexamethasone chronotherapy might be associated with lower COVID-19 mortality.

Another reason behind the timing of dexamethasone administration could have been the changes in the way COVID-19 patients were managed while the pandemic. Indeed, patients hospitalized during the second Alpha wave were more likely to be treated with dexamethasone from 16:00 h to 04:00 h (chronotherapy group) than patients managed during the first and the third waves. To address this potential source of bias we adjusted our model to the COVID-19 wave, and we also performed an analysis for the odds of death associated with chronotherapy stratified according to the COVID-19 wave (Supplementary Table 6). The stratified analysis showed that regardless of the COVID-19 wave chronotherapy always had a protective effect. This was particularly stronger in the second wave which had the highest mortality rates among hospitalized patients, and the higher blood levels of inflammatory biomarkers (Supplementary Table 7). Analysis of blood biomarkers in the different waves showed a similar trend as patients in the chronotherapy group had lower blood levels of inflammatory biomarkers than those in the control group regardless of the COVID-19 wave (Supplementary Table 8–10).

Conclusion

Among COVID-19 patients admitted to the ICU treated with dexamethasone, those who received the medication between 16:00 h and 4:00 h were associated with lower odds of death than those who received the treatment between 4:00 h and 16:00 h. These differences in odds of mortality were accompanied by differences in blood levels of inflammatory biomarkers.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12879-025-11322-6>.

Supplementary Material 1.

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Authors' contributions

M.A, A.H, H.Y and F.T contributed to the conception and study design. M.A and F.T wrote the main manuscript and prepared tables and figures. V.C contributed to data acquisition. M.A, A.H, H.A, H.Y and F.T contributed to data interpretation and analysis. All authors reviewed and approved the manuscript.

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Data availability

Data is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of Hamad Medical Corporation (Protocol number: MRC-01–20-145) with a waiver of informed consent under the pandemic response framework. All methods used in this study were conducted by the relevant guidelines and regulations (such as the Declaration of Helsinki).

Competing interests

The authors declare no competing interests.

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