Cohort Study

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Deferoxamine in the management of COVID-19 adult patients admitted to ICU: a prospective observational cohort study

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Background: COVID-19 infection is associated with high mortality, and despite extensive studying the scientific society is still working to find a definitive treatment. Some experts postulated a beneficial role of Deferoxamine.
Aim: The aim of this study was to compare the outcomes of COVID-19 adult patients admitted to the ICU who received deferoxamine to those who received standard of care.
Methods: Prospective observational cohort study, in the ICU of a tertiary referral hospital in Saudi Arabia to compare all-cause hospital mortality between COVID-19 patients who received deferoxamine and standard of care.
Results: A total of 205 patients were enrolled, with an average age of 50.1 ± 14.3, 150 patients received standard of care only, and 55 patients received deferoxamine additionally. Hospital mortality was lower in deferoxamine group (25.5 vs. 40.7%, 95% CI = 1.3–29.2%; $P = 0.045$). Clinical status score upon discharge was lower in deferoxamine group (3.6 ± 4.3 vs. 6.2 ± 4, 95% CI: 1.4–3.9; $P < 0.001$), as was the difference between discharge score and admission score (indicating clinical improvement). More patients admitted with mechanical ventilation were successfully extubated in the deferoxamine group (61.5 vs. 14.3%, 95% CI: 15–73%; $P = 0.001$), with a higher median ventilator-free days. There were no differences between groups in adverse events. Deferoxamine group was associated with hospital mortality [odds ratio = 0.46 (95% CI: 0.22–0.95); $P = 0.04$].
Conclusions: Deferoxamine may have mortality and clinical improvement benefits in COVID-19 adults admitted to ICU. Further powered and controlled studies are required.

Keywords: COVID-19, critically ill, deferoxamine, mortality

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HIGHLIGHTS

- To our best knowledge, this is the first clinical trial to evaluate the effects of deferoxamine on COVID-19 adult critically ill patients.
- Deferoxamine was associated with lower all-cause hospital mortality rate.
- Deferoxamine group showed improvement of clinical status, more frequent extubation, and ventilator-free days (VD).
- Larger randomized clinical trials are required to ascertain the benefits of deferoxamine in COVID-19 patients.

Introduction

More than 2 years since the first cases of viral pneumonia caused by a novel coronavirus emerged from China[1], the worldwide spread of the COVID-19 viral infection, and its declaration as a pandemic by the WHO[2]. Apart from the protective benefits of highly efficacious vaccines developed by different companies[3], no definite treatment of COVID-19 is approved or recommended, perhaps with the exception of remdesivir and dexamethasone in certain conditions[4].

Recently, several publications postulated a possible beneficial role of iron-chelating agents, particularly deferoxamine, in the treatment of COVID-19 patients[5–8]. The authors of those commentaries and reviews built their hypotheses on understanding of pathophysiologic mechanisms, such as formation of a complex with porphyrin by COVID-19 virus dissociating iron[6], the increased serum iron is implicated in the induction of oxidative stress due to the formation of reactive oxygen species, which may lead to lung damage and deterioration of pulmonary functions[8]. Reactive oxygen species also cause an upregulation of proinflammatory mediators such as interleukin (IL) 1B, IL-6, and tumor necrosis factor-α[9]. Furthermore, iron may be required for viral replication of COVID-19 as it is the case for other RNA viruses[10], and chelating iron may reduce viral replication. Consequently, deferoxamine, an iron-chelating agent approved for the treatment of iron overload, may have a beneficial impact on COVID-19 patients. In addition to its possible role in immune-modulation, as seen as the upregulation of B-lymphocytes and neutralizing antibody titers in animal models[11,12]. No matter how compelling these hypotheses are, they remain opinions of their authors, based solely on in vitro observations, or at best animal models' results. Clinical studies of any design are currently lacking, with regards to the role of deferoxamine in the management of COVID-19 infection, and the only available patients' data are those that correlate serum iron levels, or ferritin levels with the severity or outcomes of COVID-19 patients[13].

Intrigued by the promising role of deferoxamine, we conducted this study under the hypothesis that deferoxamine may improve outcomes of COVID-19 patients, with the main aim of comparing all-cause hospital mortality between patients who receive deferoxamine and those who do not.

Methods

This was a single-center prospective observational cohort study conducted at the ICU of King Saud Medical City (KSMC), Riyadh, Saudi Arabia. KSMC is the largest government hospital in the central region of Saudi Arabia. It has a capacity of 1200 inpatient beds, the ICU originally included 100 beds but was expanded during the COVID-19 pandemic to include 127 beds, half of which are single-room beds, and the rest are open cohorting areas. All ICU beds are fully equipped with capabilities of invasive and noninvasive monitoring and Ventilation. The ICU is run 24/7 by intensivists, with a 1:1 nurse-to-patient ratio. During the COVID-19 pandemic, KSMC became the tertiary referral center of positive cases, only transferring stabilized patients to other hospitals when there were boarding new cases in the emergency department. The ICU generally follows the COVID-19 management guidelines issued by the Saudi Ministry of Health[14]. The study was conducted between 1 October and 31 December 2021. The work has been reported in line with the STROCSS criteria[15] (Supplemental Digital Content 1, http://links.lww.com/MS9/A65).

Inclusion and exclusion criteria

Any patient admitted to the ICU during the study period was eligible for enrollment, as long as they fulfilled the following criteria: At least 18 years of age, confirmed positive COVID-19 infection by reverse transcriptase PCR through a nasopharyngeal swab within less than seven days, in addition to at least one of the following:

- Peripheral oxygen saturation less than 90% for 10 min on room air.
- Respiratory rate more than 30/min.
- Partial pressure of oxygen to fraction of inspired oxygen ratio (P/F ratio) less than 300.
- Requirement of supplemental oxygen to maintain oxygen saturation of at least 95%, through nasal cannula, face mask, nonrebreathing mask, or high flow nasal oxygen.
- Noninvasive mechanical ventilation, including biphasic or continuous positive airway pressure.
- Invasive mechanical ventilation via endotracheal intubation or tracheostomy tube.

We excluded pregnant or lactating women, known cases of HIV, known cases of pulmonary tuberculosis, history of receipt of deferoxamine within the last 6 months, refusal to participate in the trial, admitted to ICU with Do Not Resuscitate (DNR) order or expected to die within 24 h of ICU admission according to the treating consultant intensivist. We divided enrolled patients into two groups, the deferoxamine group, and standard of care (SOC) group.

Outcomes

The primary outcome was the percentage of all-cause hospital mortality between the deferoxamine and SOC groups. Whereas, secondary outcomes included ICU length of stay (LOS), hospital LOS, newly grown bacterial cultures (from any source), any adverse events (defined in Supplementary File, Supplemental Digital Content 2, http://links.lww.com/MS9/A66), and the difference of clinical status of the patients between ICU admission and hospital discharge according to progression scale previously used[16] (details in Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/MS9/A66), calculated as the clinical status of hospital discharge minus that of ICU admission (higher differences indicate worsening). Other subgroup outcomes were the need for endotracheal intubation (for patients admitted spontaneously breathing), and successful extubation and VFD (for patients admitted on invasive mechanical ventilation). Patients transferred to other healthcare facilities were censored at discharge and were not followed further.

Patients' management

In this prospective observational study, the decision to administer deferoxamine (or not) to any of the enrolled patients was entirely up to the treating consultant intensivist, the study team had absolutely no role in the treatment assignment, we only kicked off the study period with a journal club, where we discussed and presented the various publications postulating a beneficial effect of deferoxamine in the management of COVID-19 patients, but afterwards, the team never interfered with decisions of the treating consultant. Apart from deferoxamine, all COVID-19 patients received the SOC, as per the ICU protocols.

Deferoxamine regimen

In our ICU, deferoxamine is administered as a loading dose of 1000 mg by intravenous infusion, diluted in sterile water for injection (500 mg/5 ml water), and a rate of infusion of 15 mg/kg/h. To be followed after four hours by a total of four doses of 500 mg (administered similarly to the loading dose) every four hours.

Data management

De-identified data were recorded for all enrolled patients, including demographics (age, sex, body weight, comorbidities, and smoking status), presenting complains, clinical status score upon ICU admission and hospital discharge, supplemental oxygen requirement, the need of intubation for spontaneously breathing patients, or extubation for mechanically ventilated patients and the duration since extubation to hospital discharge, ICU and hospital LOS, hospital outcome, initial laboratory investigations upon ICU admission (including hemoglobin, total white blood cell count, platelets count, serum creatinine, liver function tests, serum lactate, serum ferritin, in addition to Sequential Organ Failure Assessment (SOFA) score upon ICU admission. Missing data were completed by multiple imputation method.

Statistical plan

Continuous variables were summarized as mean ± SD as well as median and interquartile range. Discrete variables were summarized as frequency and percentage. We compared continuous variables between groups by Student *t*-test or Wilcoxon rank-sum test as appropriate. If the Student *t*-test was used for the comparison, we accounted for unequal variance due to differences in group sizes (Welch *t*-test). Discrete variables were compared between groups by chi-square test or Fisher's exact test as appropriate.

As a sensitivity test for the primary outcome, we performed logistic regression for in-hospital mortality, using the backward elimination method (if $P > 0.15$) to retain significant predictors in the model, and presented its results as odds ratio with corresponding 95% CI, we explored goodness of fit of the model by Hosmer–Lemeshow test, and examined fulfillment of logistic regression assumptions by Box–Tidwell test for linearity of the logit of the outcome and continuous predictors, as well as correlation coefficients of independent variables for the absence of multicollinearity. Furthermore, we visually presented the survival of patients in both groups (censored at hospital discharge) by Kaplan–Meier curve, along with log-rank test *P*-value.

Potential bias of the study outcomes may arise by the fact that we considered all patients transferred to other hospitals as 'Alive' discharge, accordingly, we performed three hypothetical scenarios, best case scenario, worst-case scenario, and equivocal case scenario (details in Supplementary File, Supplemental Digital Content 2, http://links.lww.com/MS9/A66).

We did not calculate a sample size as we intended to enroll all eligible patients within the study period, and there was no correction for multiple testing. All statistical tests were considered significant if *P*-values were less than 0.05. Commercially available statistical software (STATA) was used in all statistical tests (StataCorp. 2019, Stata Statistical Software: Release 16; StataCorp LLC).

Ethical Considerations

The study was approved by the local institutional review board (under the registration number: H1RI-16-Jul20-04). Written informed consent was signed by all enrolled patients or their legal guardians for the enrollment in the study and data collection, but not treatment assignment, as that was at the discretion of the treating consultant. The study was retrospectively registered at Research Registry (http://www.researchregistry.com) under UIN: (researchregistry8652) and follows the general principles outlined by the declaration of Helsinki.

Results

During the study period, we screened 317 COVID-19 admissions to the ICU, we excluded 112 patients, while 205 patients were enrolled in the study. Figure 1 shows enrollment flow and reasons of exclusion. 150 patients received the SOC and 55 patients received deferoxamine and SOC at the discretion of the treating consultant. The deferoxamine group included a higher percentage of males and presented more frequently with cough (Table 1). Otherwise, both groups were similar. Deferoxamine group had a mean age of 52.2 ± 14.1 years compared with a mean age of 49.4 ± 14.4 years for the SOC group. We observed a statistically nonsignificant higher percentage of mechanically ventilated patients in SOC group, and the distribution of received medications (other than deferoxamine) was similar between both groups. Missing data were mainly of lab investigations, with a maximum percentage of 9.8% missing for neutrophils, data were completed by multiple imputations (Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/MS9/A66).

Outcomes

The primary outcome of in-hospital mortality was significantly different between both groups, sixty one patients (40.7%) died in the hospital from the SOC group, as compared with 14 patients (25.5%) of the deferoxamine group ($P = 0.045$, 95% CI: 1.3–29.2%). (Table 2). All in-hospital mortalities took place in the ICU, and all patients underwent cardiopulmonary resuscitation. Notably, more patients were transferred to other hospitals in the SOC group, and were considered alive at hospital discharge (Supplementary Table S3, Supplemental Digital Content 2, http://links.lww.com/MS9/A66). The hypothetical case scenarios indicate significantly lower mortality of the deferoxamine group in the best and equivocal scenarios, whereas, the worst-case scenario showed numerically lower mortality for the deferoxamine group, however, it was not statistically significant (Supplementary Table S4, Supplemental Digital Content 2, http://links.lww.com/MS9/A66).

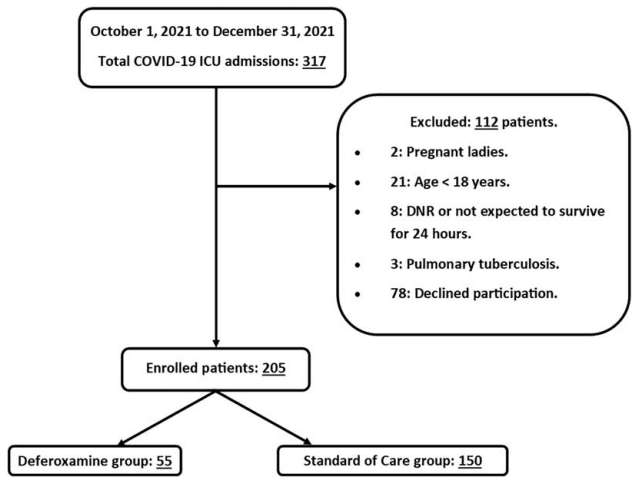

Figure 1. Patients' enrollment flow diagram.

Table 1

Demographic and clinical characteristics of included patients

Variables	Overall ($N=205$)	SOC ($n=150$)	Deferoxamine ($n=55$)	P
Age (years)	50.1 ± 14.3	49.4 ± 14.4	52.2 ± 14.1	0.2
	49 (40–58)	49 (40 –58)	52 (41–63)	
Sex				
Males	183 (89.3)	129 (86)	54 (98.2)	0.02
Females	22 (10.7)	21 (14)	1 (1.8)	
Ethnicity				0.3
Saudi	29 (14.1)	19 (12.7)	10 (18.2)	
Non-Saudi	176 (85.9)	131 (87.3)	45 (81.8)	
Body weight (kg)	78 ± 13.7	77.6 ± 12.5	78.9 ± 16.7	0.8[a]
	79 (70–85)	79.5 (70–85)	79 (70–85)	
Smoker	63 (30.7)	47 (31.3)	16 (29.1)	0.8
Symptoms				
SOB	189 (92.2)	135 (90)	54 (98.2)	0.1
Fever	156 (76.1)	109 (72.7)	47 (85.5)	0.09
Cough	106 (51.7)	57 (36.8)	49 (89.1)	< 0.001
Chest pain	24 (11.7)	19 (12.7)	5 (9.1)	0.5
Altered consciousness	4 (2)	4 (2.7)	0 (0)	0.5
GIT symptoms	16 (7.8)	12 (8)	4 (7.3)	0.9
Comorbidities				
diabetes mellitus	73 (35.6)	50 (33.3)	23 (41.8)	0.3
Hypertension	54 (26.3)	37 (34.7)	17 (30.1)	0.4
Ischemic heart disease	5 (2.4)	4 (2.7)	1 (1.8)	0.7
Chronic lung disease	2 (1)	1 (0.7)	1 (1.8)	0.4
Chronic kidney disease	1 (0.5)	1 (0.7)	0 (0)	0.5
Malignancy	9 (4.4)	7 (4.7)	2 (3.6)	0.9
SOFA score	4.4 ± 1.6	4.3 ± 1.5	4.7 ± 1.6	0.1
	4 (3–5)	4 (3–5)	5 (3–6)	
Ordinal scale of ICU	5.8 ± 1	5.9 ± 1	5.7 ± 1	0.2[a]
admission	5 (5–7)	5.5 (5–7)	5 (5–6)	
Mode of ventilation				
MV	69 (33.7)	56 (37.3)	13 (23.6)	0.09
BiPAP/CPAP	13 (6.3)	7 (4.7)	6 (10.9)	0.2
HFNC	16 (7.8)	12 (8)	4 (7.3)	0.9
NRM	67 (32.7)	45 (30)	22 (40)	0.2
FM	30 (14.6)	23 (15.3)	7 (12.7)	0.8
NC	10 (4.9)	7 (4.7)	3 (5.5)	0.9
Labortaory investigations				
Hemoglobin (g/dl)	12.4 ± 2.2	12.3 ± 2.3	12.6 ± 1.9	0.3
	12.5 (11–13.9)	12.1 (10.9–13.8)	12.8 (11.1–14.2)	
WBC (10^9/l)	14 ± 5.6	14.3 ± 5.4	13.1 ± 5.8	0.2[a]
	13 (10.1–16.1)	13.2 (10.7–16)	12.2 (8.6–17.2)	
Lymphocytes (10^9/l)	9.5 ± 11.9	8.5 ± 11.2	11.9 ± 13.3	0.01[a]
	6.6 (2–13.3)	6.2 (1.2–13.1)	8.7 (5.5–14.3)	
Neutrophils (10^9/l)	6.8 ± 1.4	6.8 ± 1.4	6.8 ± 1.3	0.9
	6.7 (5.8–7.7)	6.7 (5.8–7.7)	6.7 (5.8–7.7)	
Platelets (10^9/l)	280.6 ± 102.6	281.3 ± 101.3	278.8 ± 106.8	0.9[a]
	261 (214–336)	261.5 (215 –336)	260 (201–340)	
aPTT (s)	37.6 ± 25.4	38.3 ± 26	35.7 ± 24	0.2
	33.1 (27.3–40.8)	34.3 (27.8–41.3)	30.3 (26.4–37.5)	
PT (s)	13.3 ± 3.2	13.2 ± 3.3	13.5 ± 2.6	0.7
	13.4 (11.7–12.6)	13.5 (11.8–14.8)	12.8 (11.5–14.9)	
AST (U/l)	29.1 ± 12.1	29.2 ± 12.1	29.5 ± 10.2	0.8
	28.7 (21.5–36.4)	29.3 (21.5–36.5)	28.1 (22.1–36.9)	
ALT (U/l)	27.6 ± 7.7	27.7 ± 7.9	28.2 ± 7.1	0.6
	28 (22.4–32.5)	28 (22.2–32.8)	28.1 (24–31.9)	
Creatinine (μmol/l)	1.2 ± 0.4	1.17 ± 0.4	1.13 ± 0.4	0.4
	1.2 (0.9–1.4)	1.2 (0.9–1.5)	1.2 (0.9–1.3)	
Lactate (mmol/l)	3.4 ± 0.5	3.4 ± 0.5	3.4 ± 0.5	0.3
	3.4 (3.1–3.7)	3.4 (3.1–3.8)	3.3 (3–3.7)	
Ferritin (μ/l)	1265.8 ± 66.7	1268.7 ± 60.5	1265.7 ± 69.4	0.1[a]
	1206 (843–1699)	1178.7 (811.6–1786.3)	1261.5 (1219–1308)	

Table 1

(*Continued*)

Variables	Overall ($N=205$)	SOC ($n=150$)	Deferoxamine ($n=55$)	P
Received medications				
Steroids	141 (68.8)	102 (68)	39 (71)	0.8
Antibiotics	169 (82.4)	123 (82)	46 (83.6)	0.9
Antiviral	90 (43.9)	64 (42.7)	26 (47.3)	0.7
Tocilizumab	14 (6.8)	11 (7.3)	3 (5.5)	0.9

Continuous variables are represented as mean ± SD and median (interquartile range); discrete variables are represented as *n* (%).

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BiPAP, biphasic positive airway pressure; CPAP, continuous positive airway pressure; FM, face mask; GIT, gastrointestinal tract; HFNC, high flow nasal cannula; MV, mechanical ventilation; NC, nasal cannula; NRM, nonrebreathing mask; PT, prothrombin time; SOB, shortness of breath; SOC, standard of care; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell count.

[a]Wilcoxon rank-sum test (non-normal distribution) All *t*-tests assume unequal variance.

The secondary outcomes showed a significantly higher clinical status score upon discharge in the SOC group compared with deferoxamine group (6.2 ± 4 vs. 3.6 ± 4.3, 95% CI: 1.4–3.9, $P < 0.001$). Likewise, the difference between the clinical status score upon hospital discharge and ICU admission was higher in the SOC group compared with deferoxamine group (0.3 ± 3.7 vs. − 2.2 ± 4.2, 95% CI: 1.3–3.7; $P < 0.001$). There were no significant differences between both groups with regards to ICU LOS, hospital LOS, grown bacterial cultures, and adverse events (Table 2 and Supplementary Table S5, Supplemental Digital Content 2, http://links.lww.com/MS9/A66).

Subgroup analysis

In the SOC group, 94 patients were admitted to ICU spontaneously breathing, 31 of them (30%) required intubation during their ICU stay, whereas 10 patients (23.8%) required intubation (out of 42 admitted spontaneously breathing in the deferoxamine group), there was no significant difference between both intubation rates (95% CI: − 9 to 25%; $P = 0.4$). However, the successful extubation rate was significantly higher in deferoxamine group compared with SOC group, 61.5 and 14.3%, respectively (95% CI: 15–73%; $P = 0.001$). Successfully extubated patients in deferoxamine group had significantly longer VFD compared with SOC group (3.7 ± 3.8 vs. 1 ± 2.7, 95% CI: − 4.5 to − 0.9; $P < 0.001$).

Table 2

Primary and secondary outcomes

Outcome	SOC ($n=150$)	Deferoxamine ($n=55$)	P (95% CI of difference)
Hospital mortality	61 (40.7)	14 (25.5)	0.045 (1.3–29.2%)
ICU LOS (days)	10.1 ± 7.1 9 (5–13)	12.2 ± 8.7 10 (6–14)	0.15[a] (− 4.4 to 0.3)
Hospital LOS (days)	14.2 ± 8.3 13 (8–19)	16.6 ± 10.3 14 (9–22)	0.22[a] (− 5.1 to 0.4)
Ordinal scale of discharge	6.2 ± 4 7 (3–10)	3.6 ± 4.3 0 (0–10)	< 0.001[a] (1.4–3.9)
Difference in ordinal scale	0.3 ± 3.7 1.5 (− 4 to 3)	− 2.2 ± 4.2 − 5 (− 5 to 3)	< 0.001[a] (1.3–3.7)
Required intubation (out of not intubated on admission)	31/94 (33)	10/42 (23.8)	0.4 (− 9 to 25%)
Extubated (out of initially intubated)	8/56 (14.3)	8/13 (61.5)	0.001 (15–73%)
Ventilator-free days (postextubation)	1 ± 2.7 0 (0–0)	3.7 ± 3.8 3 (0–6)	< 0.001[a] (− 4.5 to − 0.9)
Cultures grown	13 (8.7)	5 (9.1)	0.9 (− 8 to 12%)
Adverse events (other than death)	8 (5.3)	6 (10.9)	0.3 (− 2.8 to 17.3%)

Continuous variables are represented as mean ± SD and median (interquartile range); discrete variables are represented as *n* (%).

LOS, length of stay; SOC, standard of care.

[a]Wilcoxon rank-sum test (non-normal distribution) All *t*-tests assume unequal variance.

The multivariable logistic regression model showed that being in the deferoxamine group is associated with decreased odds of hospital mortality [odds ratio = 0.46 (95% CI: 0.22–0.95); $P = 0.04$], other significant variables retained in the model were age and mechanical ventilation upon ICU admission. The model was well fitted (Hosmer–Lemeshow $P = 0.3$), with fulfilled assumptions of logistic regression (Table 3 and Supplementary Tables S6–S8, Supplemental Digital Content 2, http://links.lww.com/MS9/A66 and Supplementary Figs. S1, S2, Supplemental Digital Content 2, http://links.lww.com/MS9/A66).

Kaplan–Meier curve of survival (Fig. 2) shows a significantly higher survival of patients in the deferoxamine group compared with the SOC group (log-rank test $P = 0.009$), the median survival of patients in deferoxamine group was 40 days (95% CI: 24–40 days), whereas that of patients in the SOC group was 22 days (95% CI: 17–31 days).

Discussion

In this study we found a lower hospital mortality rate in the deferoxamine group compared with SOC group, the deferoxamine group had a reduction in the ordinal scale of clinical status from admission to discharge, which was significantly lower at discharge compared with SOC group, indicating clinical improvement. More patients in the deferoxamine group were successfully extubated with more VFD. There were no differences between groups in ICU and hospital LOS, the requirement of intubation, newly grown cultures, and adverse events. Deferoxamine was associated with a reduction of mortality odds by 54% in a well-fitted multivariable logistic regression model adjusted for age and mechanical ventilation status upon ICU admission.

Deferoxamine, an iron-chelating agent, possibly ameliorates the consequences of COVID-19 infection and mitigates the cascade of events that ultimately lead to clinical deterioration and death. Beginning with the reduction of viral replication, deferoxamine reduces the available iron needed for viral replication, as was observed with other RNA viruses such as HIV type 1[17].

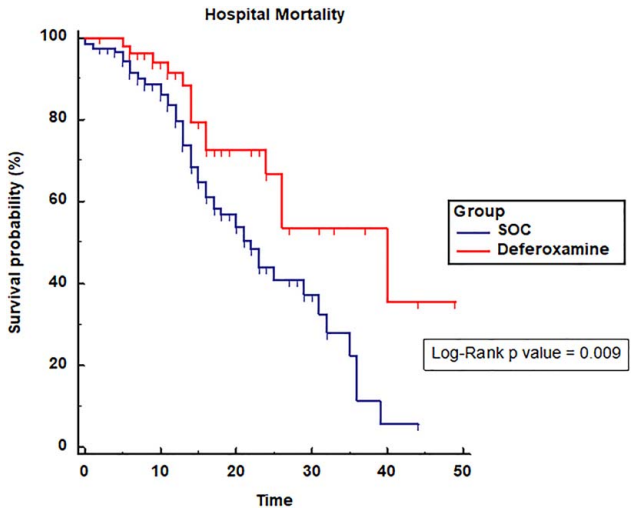

Figure 2. Survival analysis of both groups. Deferoxamine group median survival = 40 days (95% CI: 24–40 days) SOC group median survival = 22 days (95% CI: 17–31 days). SOC, standard of care.

Dysregulated immune response and hyperinflammation are commonly implicated in the pathophysiology of severe forms of COVID-19 infection and multiple organ failure and are almost always associated with high levels of proinflammatory cytokines such as IL-6[18], deferoxamine may have a role in reducing IL-6 as well as other cytokines, subsequently preventing patients' deterioration and development of lung injury as seen in animal models[19], and in vitro studies on closely related viruses such as influenza A virus[9]. High levels of iron increase the production of reactive oxygen species[5], which impose an oxidative stress that promotes the development of acute respiratory distress syndrome[20], a characteristic picture of severe cases of COVID-19 infection[21].

This study to our best knowledge is the first to explore patient-centered outcomes in COVID-19 patients who received deferoxamine, and our results seem to be in agreement with the hypotheses of its beneficial role. There was a significantly lower mortality rate in the deferoxamine group in our study, and despite being barely significant, and in view of an obvious underpower, this result may not be conclusive. However, it should be taken in account that the mortality rate in the SOC group may have been underestimated by the higher proportion of patients transferred to other hospitals and subsequently censored in that group, as evident by the best and equivocal hypothetical case scenarios. Accordingly, this lower mortality rate in the deferoxamine group at least can be considered as idea generating for further investigations in an adequately powered controlled trial, since the mortality difference was not statistically significant in the worst-case scenario. Furthermore, we observed more successful liberations from mechanical ventilation with more VFD, as well as clinical improvement evident by the reduction of the clinical status score in the intervention group. Both, observations could be interpreted in view of the proposed ability of deferoxamine to ameliorate tissue inflammation. Receiving deferoxamine was associated with a substantial reduction of mortality odds, again, possibly reflecting its role in downregulating IL-6 and other proinflammatory cytokines implicated in the development of acute respiratory distress syndrome, patients' deterioration, and death.

We believe that our study could be the building foundation to investigate a new frontier in the management of COVID-19, despite its numerous limitations. This was an observational single-center study, carrying all the inherent limitations of such designs, mainly the lack of randomization. The small sample size undoubtedly renders the study underpowered. We cannot definitely exclude confounding effects either of patients' characteristics or other modalities of treatment, due to the uncontrolled nature of the study, such as the vaccination status of enrolled patients which we did not record in our study, or the different modalities of supplemental oxygen when patients were spontaneously breathing. We cannot be sure if the wide spectrum of clinical severity of enrolled patients has undermined or exaggerated the results of the study, as we did not perform subgroup analyses by admission severity in view of the small numbers in each subset that would have made any statistical comparison meaningless.

Table 3

Multivariable logistic regression

Variables	OR (95% CI)	*P*
Deferoxamine group	0.46 (0.22–0.95)	0.04
Age	1.03 (1.01–1.05)	0.01
Sex	0.41 (0.13–1.25)	0.12
MV upon admission	2.6 (1.4–4.8)	0.003

The model correctly classifies 68.2% of cases. Hosmer–Lemeshow $P = 0.3$ (well-fitted model). Assumption of linearity between logit (outcome) and predictor variables fulfilled (Box–Tidwell $P = 0.2$). MV, mechanical ventilation; OR, odds ratio.

Conclusions

Deferoxamine could decrease mortality and improve clinical evolution in adult COVID-19 patients admitted to ICU. We recommend further exploration of the role of deferoxamine in the management of COVID-19, in adequately powered controlled trials (Table 3).

Ethical approval

This study was approved by the institutional review board of King Saud Medical City, Riyadh, Saudi Arabia, under number H1RI-16-Jul20-04. All participants or their legal guardians signed an informed consent form.

Consent

Written informed consent was signed by all enrolled patients or their legal guardians.

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Author contribution

Conceptualization: A.M.A., A.F.M., Z.A.M. Methodology: A.M.A., A.F.M., Z.A.M., S.A., W.T.A. Formal analysis: A.S.B., W. T.A., B.A. Validation: L.A., S.A.M., Z.A.-H., M.A.A.-O., W.T.A. Resources: A.S.B., B.A., H.M., M.A.A.-O. Data curation: H.M.,

W.T.A., M.A. Writing – original draft: A.M.A., A.F.M., Z.A.M., W.T.A. Writing – review and editing: S.A., A.S.B., B.A., S.A.M., Z. A.-H.,M.A.A.-O., H.M., M.A. Visualization: A.F.M., W.T.H. Supervision: A.M.A. Project administration: A.M.A., Z.A.M.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: researchregistry.
2. Unique Identifying number or registration ID: researchregistry8320.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home

Guarantor

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Data availability statement

Data generated during this study and used in the analysis is available with the corresponding author upon reasonable request.

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