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The Impact of Recombinant Human Erythropoietin Administration in Critically ill COVID-19 Patients: A Multicenter Cohort Study

Khalid Al Sulaiman, BCCCP, BCNSP, MBA, FCCM[1,2,3,4], Ohoud Aljuhani, Pharm.D, BCCCP[5], Ghazwa B. Korayem, Pharm.D[6], Ali F. Altebainawi, Pharm.D[7,8], Ramesh Vishwakarma, PhD[9], Mashael AlFaifi, Pharm.D[10], Samiah Alsohimi, Pharm.D[11,12], Aljoharah Alrayes, Pharm.D[6], Sara Albishi, Pharm.D[6], Reem Alqahtani, Pharm.D[6], Mai Alalawi, Pharm.D[13,14], Ibrahim Al Sulaihim, MSc[15], Thamer A. Alanazi, BSc[16], Rahaf A. Alqahtani, Pharm.D[1], Alaa Almagthali, Pharm.D[12], Shahamah Jomah, BSc[17], Areej Alshlowi, BSc[18], Tahani R. Alshammari, BSc[7], Shahad S. Alzahrani, Pharm.D[2], and Marwa I. Abdulqader, Pharm.D[2]

Abstract

The use of erythropoietin-stimulating agents (ESAs) as adjunctive therapy in critically ill patients with COVID-19 may have a potential benefit. This study aims to evaluate the effect of ESAs on the clinical outcomes of critically ill COVID-19 patients. A multicenter, retrospective cohort study was conducted from 01-03-2020 to 31-07-2021. We included adult patients who were ≥ 18 years old with a confirmed diagnosis of COVID-19 infection and admitted to intensive care units (ICUs). Patients were categorized depending on ESAs administration during their ICU stay. The primary endpoint was the length of stay;

[1] Pharmaceutical Care Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia
[2] College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[3] King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[4] Saudi Critical Care Pharmacy Research (SCAPE) Platform, Riyadh, Saudi Arabia
[5] Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia
[6] Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia
[7] Pharmaceutical Care Services, King Salman Specialist Hospital, Hail Health Cluster, Ministry of Health, Hail, Saudi Arabia
[8] Department of Clinical Pharmacy, College of Pharmacy, University of Hail, Hail, Saudi Arabia
[9] Norwich Medical School, University of East Anglia, Norwich, UK
[10] Pharmaceutical Care Department, King Saud Medical City, Riyadh, Saudi Arabia
[11] Pharmaceutical Care Services, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia
[12] Pharmaceutical Care Services, King Abdulaziz University Hospital, Jeddah, Saudi Arabia
[13] Department of Pharmaceutical Sciences, Fakeeh College for Medical Sciences, Jeddah, Saudi Arabia
[14] Pharmaceutical Care Department, King Abdulaziz Medical City, Jeddah, Saudi Arabia
[15] Pharmaceutical Care Department, Presidency of State Security, Central Security Hospital, Riyadh, Saudi Arabia
[16] Respiratory Therapy Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia
[17] Pharmaceutical Care Department, Dr Sulaiman Al-Habib Medical Group, Riyadh, Saudi Arabia
[18] Department of Pharmacy Practice, College of Pharmacy, Almaarefa University, Riyadh, Saudi Arabia

Corresponding Author:
Khalid Al Sulaiman, King Abdulaziz Medical City (KAMC)–Ministry of National Guard Health Affairs (MNGHA), King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, PO Box 22490, 11426 Riyadh, Saudi Arabia.
Email: alsulaimankh@hotmail.com

other endpoints were considered secondary. After propensity score matching (1:3), the overall included patients were 120. Among those, 30 patients received ESAs. A longer duration of ICU and hospital stay was observed in the ESA group (beta coefficient: 0.64; 95% CI: 0.31-0.97; $P = < .01$, beta coefficient: 0.41; 95% CI: 0.12-0.69; $P = < .01$, respectively). In addition, the ESA group's ventilator-free days (VFDs) were significantly shorter than the control group. Moreover, patients who received ESAs have higher odds of liver injury and infections during ICU stay than the control group. The use of ESAs in COVID-19 critically ill patients was associated with longer hospital and ICU stays, with no survival benefits but linked with lower VFDs.

Keywords
critically ill, COVID-19, erythropoietin-stimulating agents, ESA, length of stay, mortality, ventilator-free days (VFDs)

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Introduction

The COVID-19 pandemic has resulted in approximately 626 million cases and 6.5 million fatalities worldwide.[1] Although the majority of patients with COVID-19 had minor symptoms,[2,3] around 14% of the reported cases of COVID-19 cases progressed to serious illness and developed complications.[3] The severity of the illness may be attributed to the inflammatory response known as the "Cytokine Storm" caused by COVID-19.[4] One of the major respiratory complications of COVID-19 is acute respiratory distress syndrome (ARDS) which exacerbates other acute inflammatory disorders like sepsis, trauma, and pneumonia.[4] Patients with ARDS frequently develop respiratory failure, requiring invasive mechanical ventilation (MV) managed at the intensive care unit (ICU).[5]

Thus, immunomodulator drugs that suppress cytokine storm and hyperinflammatory response could be a potential therapeutic choice for critically ill COVID-19.[6] Many immunomodulators have been studied for the treatment of hospitalized patients with COVID-19.[7–10] These options include interleukin-6 inhibitors (IL-6), corticosteroids, and Janus kinase (JAK) inhibitors.[7–10] In addition, the use of erythropoietin-stimulating agents (ESAs) for the treatment of severe anemia and reduced blood transfusion has been reported to have additional anti-inflammatory, immunomodulatory properties, and anti-apoptotic effects.[4] Therefore, ESA has been used in the treatment of acute lung injury induced by renal ischemia, ischemic stroke, and head trauma.[11–17]

A prospective observational study reported a lower amount of endogenous erythropoietin in mechanically ventilated critically ill patients with PaO2/FiO2 <300 which might be a risk factor for difficult extubation and poor response to anemia.[18] ESAs resistance, low level of circulating erythropoietin, and high inflammatory mediator, all can inhibit erythropoietic cellular proliferation and impairs tissue oxygenation, in critically ill patients who present with cytokines storm and hypoxia paradox.[11,14,15,17] ESA can raise hemoglobin count and, thus, strengthens the oxygen reservoir, countering hypoxia.[4] Thus, ESAs have demonstrated a beneficial role in the management of ARDS.[19,20] This effect was attained by ESAs pleiotropic effect, which protects lung integrity, improves respiration, restores homeostasis, antioxidant effect, and reduced inflammation.[17,19–22]

A case report by Hadadi et al. evaluated the use of ESAs in critically ill COVID-19 patients with severe anemia and reported improved anemia symptoms in addition to viral suppression.[23] Moreover, a case series by Begemann et al. reported that four critically ill patients with COVID-19 admitted to the ICU with respiratory failure who received ESA without blood transfusion showed improvement during hospital stay or rehabilitation.[11] On the other hand, the lack of funding has prevented the publication of the Ehrenreich et al. 2020 randomized controlled trial that examined the use of erythropoietin as an adjuvant therapy for the treatment of severe COVID-19.[4] The evidence proposed that in addition to anemia management, ESA can be used as supportive therapy in critically ill patients including patients with COVID-19.[4] The theory behind the use of erythropoietin in critically ill COVID-19 patients is the ability of ESAs to work in 3 different domains that control respiration through the brainstem, lung and phrenic nerve.[11,12]

The administration of ESAs in critically ill COVID-19 patients remains questionable due to insufficient evidence and the potential adverse effect.[14,17,24–26] Recombinant human erythropoietin used as adjunctive therapy may have potential survival benefits in critically ill patients with COVID-19.[4] Therefore, the objective of this study is to evaluate the effect of ESAs on the clinical outcomes of critically ill COVID-19 patients.

Methods

Study Design

A multicenter retrospective cohort study was conducted from 01-03-2020 till 31-07-2021 and included all adult patients who were ≥ 18 years old with a confirmed diagnosis of COVID-19 infection and admitted to ICUs. COVID-19 diagnosis was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal or throat swab testing. Critically ill patients were categorized into two sub-cohorts based on receiving ESA during ICU stay. There were no pre-defined criteria at the

participating centers for ESA use; ESA is mainly used as either a continuation of ongoing therapy or a new initiation which is based on physician clinical judgment. ESA therapy was mainly administered via the subcutaneous route of administration. All patients were followed until they were discharged or died during the in-hospital stay. The King Abdullah International Medical Research Center (KAIMRC) - Institutional Review Board approved the study in January 2021 (Ref.# NRC21R-004-01) and approved by all participating centers' internal IRB committees. All participating centers followed the same standards of care for case triaging, admission tiers, and transferring criteria. All methods were performed in accordance with relevant guidelines and regulations. Given the retrospective observational nature of the study, informed consent from the study patients was waived by the IRB committees.

Settings

This study was conducted at five hospitals in Saudi Arabia. The primary site for this study was King Abdulaziz Medical City (Riyadh), a tertiary care center, and the initial IRB approval originated from this center. Additional centers were added based on the availability of data, the center's willingness to participate, and geographic distribution, including King Abdulaziz Medical City (Jeddah), King Abdulaziz University Hospital (Jeddah), King Abdullah bin Abdulaziz University Hospital (KAAUH) (Riyadh), and King Salman Specialist Hospital (Hail).

Participants

The eligibility criteria included adult patients with confirmed COVID-19 infection through RT-PCR testing and exclusion of patients who received ESA therapy either prior to ICU admission without ICU continuation or after ICU discharge. In addition, patients were excluded if deceased within 24 h of ICU admission, had an ICU length of stay less than one day, were designated as do-not-resuscitate, or had unknown medical history. The flowchart of the study population is presented in Figure 1.

Outcomes

This study aimed to assess the association between the administration of erythropoiesis-stimulating agents and clinical outcomes in critically ill COVID-19 patients.. The primary endpoint was the LOS, while secondary endpoints were ventilator-free days (VFDs), 30-day and in-hospital mortality, and complication(s) that occurred during ICU stay (ie, new onset Afib., liver injury, all thrombosis cases, and hospital-acquired infection(s)).

Data Collection

The data collection tool was standardized among all centers. The data was collected using Research Electronic Data Capture (REDCap®) form hosted by the primary institution. The form included demographic factors, comorbidities, and clinical data, including vitals and laboratory tests (eg, lactic acid, serum creatinine, liver function tests, and inflammatory markers). The severity and clinical scores were captured within 24 h of ICU admission, such as Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Multiple Organ Dysfunction Score (MODS). Moreover, Glasgow Coma Score (GCS), acute kidney injury, proning position status, inotropes use, and the need for MV were documented within 24 h of admission. Additionally, the study recorded the early use of tocilizumab, methylprednisolone, and dexamethasone in these patients.

Statistical Analysis

Descriptive analysis was used to present the categorical variables as a number with percentage and continuous data as mean with standard deviation (SD) or median with lower (Q1) and upper (Q3) quartiles based on the distribution of data. The normality assumptions for all numerical variables were evaluated using a statistical test (the Shapiro–Wilk test) and graphical representation (ie, histograms and Q-Q plots).

The baseline characteristics of the two study groups were compared using appropriate statistical tests. Categorical variables were compared using either the Chi-square test or the Fisher exact test. On the other hand, continuous variables were compared using the Student's t-test for normally distributed data [1]. In cases where the continuous variables were not normally distributed, the Mann-Whitney U-test was utilized.

Regression analysis was done by considering the propensity score (PS) as one of the covariates in the model. Multivariable Cox proportional hazards regression analyses were performed for the 30-day and in-hospital mortality and reported using the hazard ratios (HR). The proportionality assumption was assessed before fitting the Cox model. On the other hand, multivariable logistic and negative binomial regression analysis were used for the outcomes considered in this study and reported using the odds ratios (ORs) or estimates with 95% confidence intervals (CIs) as appropriate. Model fit was assessed using the Hosmer–Lemeshow goodness-of-fit test.

In the PS-matched analysis, we selected five matching covariates, including age, baseline serum creatinine, chronic kidney disease as a comorbid condition, APACHE II score, and hematocrit at admission. Those factors were selected for their possible association with the study outcomes. A greedy nearest-neighbor matching method was used in which one patient who received ESA was matched with three patients in the control group (1:3 ratio). This eventually produces the smallest within-pair difference among all available pairs with treated patients. These patients were matched only if the difference in the logits of the PSs for pairs of patients from the two groups was less than or equal to 0.1 times the pooled estimate of the standard deviation. We considered a P-value of $< .05$ statistically significant and used SAS version 9.4 for all statistical analyses.

Results

A total of 1592 patients with confirmed COVID-19 were admitted to the ICU during the study and evaluated for inclusion. Of

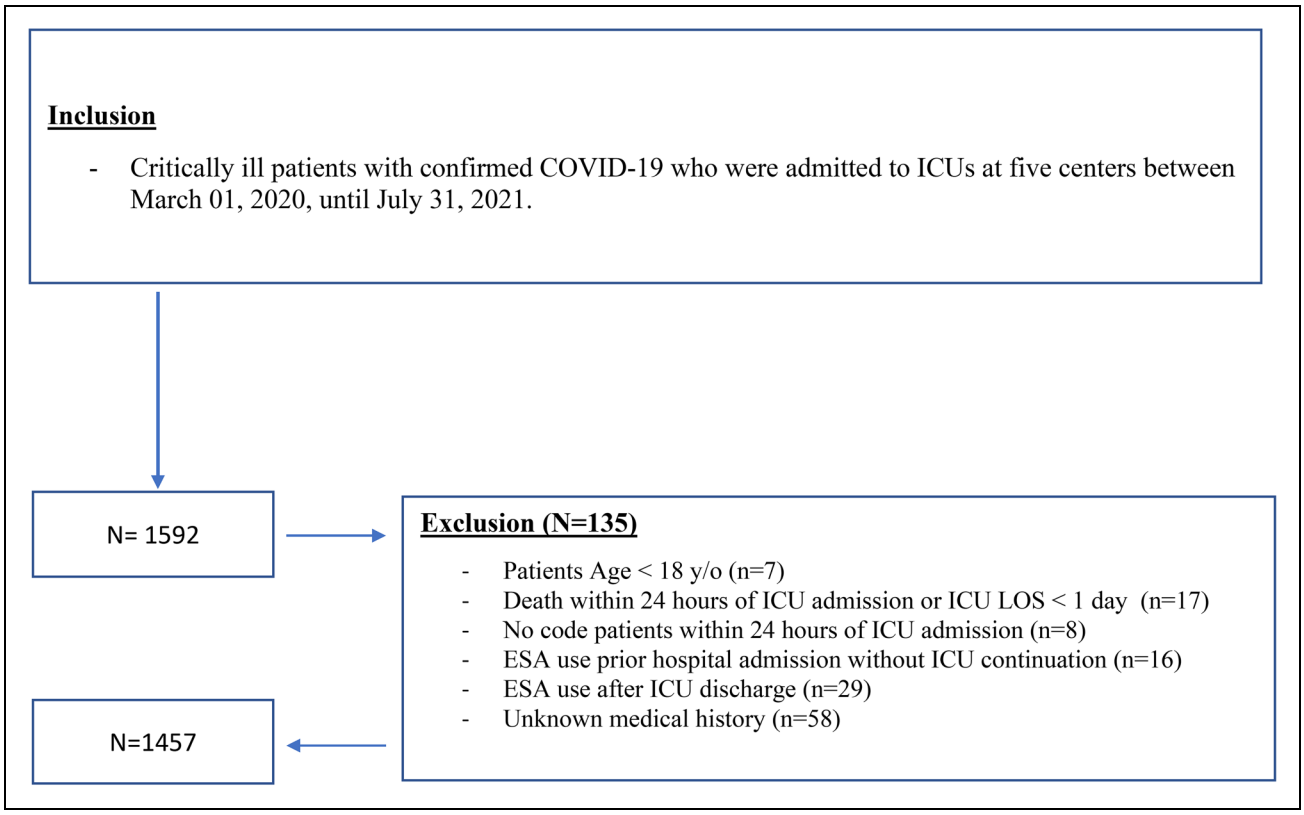

Figure 1. Flowchart for eligibility criteria.

these, 135 were excluded from the analysis due to various reasons (Figure 1). The total included number was 1457 patients, distributed as 1424 in the control group and 33 patients in the ESA group. After PS score matching (1:3) based on the predefined criteria, the number of patients included overall was 120. Of the total number, 30 patients were administered ESA (with 47% receiving Darbepoetin alfa and 53% receiving Erythropoietin). The mean weekly dose of Darbepoetin alfa was 40 mcg with a standard deviation of 20.4, while the mean weekly dose for Erythropoietin was 10,500 units with a standard deviation of 2582. Among these patients, 23% had previously received ESA therapy before their admission to the ICU and continued to receive it during their stay, whereas 76.7% received ESA therapy as a new initiation during their ICU stay.

Demographic and Clinical Characteristics

Table 1 summarizes all the baseline characteristics before and after PS matching. In the whole cohort and before the PS matching, the mediam age of the study population was 63.0 (53.0, 73.0) years, and the majority were males (62.3%). The most observed comorbidities were diabetes mellitus (61.6%), followed by hypertension (59.1%), dyslipidemia (22%), and CKD (10.6%). Moreover, patients who received ESA therapy were older, had a higher baseline MODS, serum creatinine, acute kidney injury, INR, aPTT, and a higher prevalence of CKD and IHD compared with the control group. On the other hand, the control group had a higher baseline hematocrit, albumin, and early use of tocilizumab within 24 h of ICU admission than patients who received ESA therapy before PS matching. The two groups were comparable after conducting the PS matching, except for baseline albumin and blood glucose levels within 24 h of ICU admission.

Length of Stay and Ventilator Free Days

In crude analysis, patients who received ESA therapy had a statistically significantly longer median of ICU (18 vs. 10) and hospital LOS (20 vs. 16) compared with the control group. Moreover, generalized linear regression analysis revealed a longer duration of ICU stay as well as hospital stay in patients who received ESA compared to the control group (beta coefficient: 0.64; 95% CI: 0.31-0.97; $P = < .01$, and beta coefficient: 0.41; 95% CI: 0.12-0.69; $P = < .01$, respectively). On the other hand, the ESA group's median VFDs was statistically significantly shorter than the control group (Table 2).

30-day and in-Hospital Mortality

The 30-day and in-hospital mortality were higher in patients who received ESA therapy in comparison with the control at crude analysis (71.4% vs 50.6%; $P = .06$ and 78.6% vs

Table 1. Summary of Demography and Baseline Characteristics.

	Before propensity score (PS)				After propensity score (PS)			
Variables	Overall (N = 1457)	Control (N = 1424)	ESA use (N = 33)	*P*-value	Overall (N = 120)	Control (N = 90)	ESA use (N = 30)	*P*-value
Age (years), median (Q1,Q3)	63.0 (53.00, 73.00)	63.0 (53.00, 73.00)	67.0 (60.00, 75.00)	.0818^	66.5 (58.00, 76.00)	66.0 (57.00, 76.00)	67.0 (60.00, 75.00)	.8343^
Gender—male, n (%)	899 (62.3)	884 (62.7)	15 (45.5)	.0428^^	69 (57.5)	55 (61.1)	14 (46.7)	.1657^^
BMI, mean (SD)	31.0 (8.72)	31.0 (8.76)	30.1 (6.72)	.9993^	29.4 (6.16)	29.2 (5.85)	30.0 (7.03)	.5509*
APACHE II score at admission, median (Q1,Q3)	14.0 (9.00, 21.00)	14.0 (9.00, 21.00)	16.0 (11.00, 24.00)	.1273^	16.0 (12.00, 24.00)	16.0 (12.00, 24.00)	16.5 (12.00, 24.00)	.9395^
SOFA score at admission, median (Q1, Q3)	4.0 (3.00, 7.00)	4.0 (3.00, 7.00)	6.0 (2.00, 8.00)	.1777^	6.0 (4.00, 9.00)	6.0 (4.00, 9.00)	6.0 (2.00, 8.00)	.5288^
Multiple Organ Dysfunction Score at admission, median (Q1,Q3)	5.0 (4.00, 7.00)	5.0 (4.00, 7.00)	7.5 (5.00, 9.50)	.0381^	7.0 (5.00, 9.00)	7.0 (5.00, 9.00)	7.5 (4.00, 9.00)	.8164^
Early use of Dexamethasone within 24 h, n (%)	936 (64.2)	913 (64.1)	23 (69.7)	.5084^^	71 (59.2)	50 (55.6)	21 (70.0)	.1633^^
Early use of methylprednisolone within 24 h, n (%)	149 (10.2)	147 (10.3)	2 (6.1)	.4243**	8 (6.7)	6 (6.7)	2 (6.7)	>.9999**
Early use of tocilizumab within 24 h, n (%)	329 (22.6)	327 (23.0)	2 (6.1)	.0217^^	11 (9.2)	9 (10.0)	2 (6.7)	.5837**
Proning at admission, n (%)	347 (24.6)	341 (24.7)	6 (18.8)	.4401^^	11 (9.2)	9 (10.0)	2 (6.7)	.5837**
Serum creatinine (mmol/L) baseline	129.9 (143.64)	127.2 (141.56)	246.0 (184.45)	.0010*	128.2 (77.83, 347.50)	126.5 (74.00, 329.00)	144.0 (86.65, 400.00)	.4896^
Blood urea nitrogen (BUN) (mmol/L) baseline, median (Q1,Q3)	6.9 (4.80, 11.40)	6.9 (4.80, 11.12)	13.8 (6.80, 27.37)	<.001^	11.5 (6.10, 22.50)	11.1 (5.90, 21.00)	12.6 (6.70, 26.30)	.5648^
Acute kidney injury (AKI) baseline, n (%)	398 (27.7)	383 (27.2)	15 (45.5)	.0208^^	51 (42.5)	38 (42.2)	13 (43.3)	.9151^^
Oxygenation Index (OI), Median (Q1,Q3)	16.7 (9.22, 27.27)	17.0 (9.35, 27.27)	12.5 (8.66, 24.18)	.4432^	16.7 (6.74, 22.39)	16.8 (6.58, 22.39)	14.9 (9.21, 28.41)	.8199^
Inotropes/vasopressors use baseline, n(%)	334 (23.2)	329 (23.4)	5 (15.2)	.2664^^	32 (26.9)	27 (30.3)	5 (16.7)	.1442^^
Vasoactive Inotropic Score baseline, mean (SD)	7.8 (46.91)	8.0 (47.49)	1.8 (5.94)	.7826^	8.9 (48.86)	11.4 (56.95)	1.9 (6.21)	.4732^
Lactic acid (mmol/L) baseline, median (Q1,Q3)	1.7 (1.29, 2.42)	1.7 (1.29, 2.40)	1.5 (1.36, 2.47)	.8313^	1.5 (1.16, 2.24)	1.5 (1.15, 2.24)	1.5 (1.37, 2.19)	.6425^
Platelets count (10^9/L) baseline, median (Q1,Q3)	242.0 (189.00, 314.00)	242.0 (189.00, 314.00)	221.0 (191.00, 310.00)	.8828^	239.5 (162.50, 306.00)	239.5 (155.00, 300.00)	235.0 (191.00, 322.00)	.4652^
Total WBC (10^9/L) baseline, median (Q1,Q3)	9.3 (6.52, 12.70)	9.2 (6.52, 12.70)	10.1 (6.58, 13.23)	.4709^	9.1 (6.67, 13.22)	8.7 (6.79, 13.00)	10.3 (6.58, 13.23)	.5771^
International normalized ratio (INR), median (Q1,Q3)	1.1 (1.01, 1.20)	1.1 (1.01, 1.20)	1.2 (1.06, 1.39)	.0071^	1.1 (1.04, 1.23)	1.1 (1.03, 1.21)	1.2 (1.05, 1.36)	.2535^
activated partial thromboplastin time (aPTT) (Seconds) baseline, median (Q1, Q3)	30.0 (26.70, 33.90)	29.9 (26.60, 33.80)	32.3 (29.60, 46.90)	.0021^	32.1 (28.80, 37.05)	31.9 (27.70, 36.80)	32.7 (30.00, 47.10)	.1879^
Total bilirubin (umol/L) baseline, median (Q1,Q3)	9.1 (6.50, 13.50)	9.1 (6.50, 13.45)	9.2 (5.00, 14.40)	.5335^	8.7 (5.90, 13.10)	9.0 (6.00, 12.90)	8.2 (5.00, 14.15)	.5569^
Alanine transaminase (ALT) (U \ L) baseline, median (Q1,Q3)	37.0 (24.00, 58.00)	37.0 (24.00, 58.00)	28.0 (24.00, 49.00)	.2188^	28.0 (23.00, 45.00)	28.0 (20.00, 45.00)	28.0 (24.00, 49.00)	.4784^
	51.0 (34.00, 77.00)	52.0 (34.00, 77.00)	35.0 (27.00, 56.00)	.0076^	44.0 (32.00, 68.00)	47.0 (33.00, 71.00)	35.0 (28.00, 55.50)	.1461^

(continued)

Table 1. (continued)

Variables	Before propensity score (PS)				After propensity score (PS)			
	Overall (N = 1457)	Control (N = 1424)	ESA use (N = 33)	*P*-value	Overall (N = 120)	Control (N = 90)	ESA use (N = 30)	*P*-value
Aspartate transaminase (AST) (U \ L) baseline, median (Q1,Q3)								
Albumin (g/L) baseline , mean (SD)	32.4 (5.66)	32.5 (5.59)	26.8 (5.96)	<.0001*	30.1 (5.14)	31.3 (4.27)	26.3 (5.84)	.0002*
Hematocrit (L/L) baseline,	0.4 (0.34, 0.43)	0.4 (0.34, 0.43)	0.3 (0.27, 0.38)	.0003^	0.3 (0.07)	0.3 (0.07)	0.3 (0.08)	.9842*
Creatine phosphokinase (CPK) (U/ l) baseline , median (Q1,Q3)	167.0 (73.00, 403.00)	166.0 (72.00, 403.00)	170.0 (75.00, 467.00)	.6620^	143.0 (61.00, 343.00)	139.5 (50.00, 312.00)	170.0 (77.00, 467.00)	.8068^
C-reactive protein (CRP) (mg/l) baseline , median (Q1,Q3)	132.0 (74.00, 202.00)	132.0 (74.00, 202.00)	96.0 (74.00, 221.50)	.9659^	146.0 (81.30, 241.00)	147.0 (81.30, 234.00)	117.0 (85.00, 243.00)	.7470^
Fibrinogen level (gm/l) baseline , median (Q1,Q3)	5.5 (3.89, 7.07)	5.5 (3.89, 7.18)	5.4 (3.60, 5.66)	.6043^	5.7 (4.68, 7.21)	5.7 (4.39, 7.21)	5.5 (4.95, 6.90)	.9845^
D-dimer Level (mg/l) baseline, median (Q1,Q3)	1.3 (0.70, 3.03)	1.2 (0.69, 3.02)	1.5 (0.87, 3.38)	.2841^	1.4 (0.80, 3.34)	1.5 (0.76, 3.39)	1.4 (0.87, 2.40)	.8784^
Ferritin level (ug/l) baseline, median (Q1, Q3)	679.0 (369.40, 1531.00)	688.9 (370.80, 1546.00)	422.0 (368.00, 757.00)	.0596^	511.4 (371.20, 1432.50)	566.5 (327.00, 1951.00)	422.0 (374.40, 748.90)	.1395^
Blood glucose level (mmol/L) baseline, median (Q1,Q3)	10.9 (7.60, 15.40)	10.9 (7.61, 15.20)	11.8 (7.40, 21.70)	.0767^	12.1 (7.80, 16.80)	12.0 (7.60, 16.50)	14.7 (9.50, 22.30)	.0442^
PaO2/FiO2 ratio baseline, median (Q1, Q3)	81.2 (60.00, 130.80)	80.9 (60.00, 130.40)	95.8 (62.54, 152.60)	.3709^	95.0 (66.30, 175.70)	95.0 (71.62, 190.00)	86.7 (61.00, 130.00)	.1369^
Highest heart rate (HR) at admission, median (Q1,Q3)	102.0 (90.00, 114.00)	102.0 (90.00, 114.00)	102.0 (94.00, 113.00)	.7194^	102.5 (92.00, 112.50)	102.5 (92.00, 112.00)	103.0 (84.00, 113.00)	.6647^
Lowest MAP at admission	73.0 (63.00, 83.00)	73.0 (63.50, 83.00)	75.0 (63.00, 87.00)	.9272^	71.2 (14.59)	70.5 (14.26)	73.6 (15.53)	.3072*
Pharmacological DVT prophylaxis use during ICU stay, n (%)	1326 (91.6)	1294 (91.5)	32 (97.0)	.2630**	109 (90.8)	80 (88.9)	29 (96.7)	.2011**
Patient received nephrotoxic drugs/ material during ICU stay, n (%)*$	1235 (85.6)	1205 (85.5)	30 (90.9)	.3784**	102 (85.0)	74 (82.2)	28 (93.3)	.1399**
Comorbidity, n (%)								
Atrial fibrillation (A Fib)	63 (4.3)	61 (4.3)	2 (6.1)	.6198**	6 (5.0)	4 (4.4)	2 (6.7)	.6286**
Heart failure	120 (8.2)	115 (8.1)	5 (15.2)	.1438**	16 (13.3)	12 (13.3)	4 (13.3)	>.9999**
Hypertension	861 (59.1)	836 (58.7)	25 (75.8)	.0489^^	87 (72.5)	65 (72.2)	22 (73.3)	.9060^^
Diabetes mellitus	898 (61.6)	873 (61.3)	25 (75.8)	.0915^^	86 (71.7)	63 (70.0)	23 (76.7)	.4828^^
Dyslipidemia	321 (22.0)	314 (22.1)	7 (21.2)	.9085^^	30 (25.0)	24 (26.7)	6 (20.0)	.4652^^
Ischemic heart disease (IHD)	148 (10.2)	141 (9.9)	7 (21.2)	.0335**	23 (19.2)	16 (17.8)	7 (23.3)	.5032^^
Chronic kidney disease (CKD)	154 (10.6)	137 (9.6)	17 (51.5)	<.0001**	56 (46.7)	42 (46.7)	14 (46.7)	>.9999^^
Cancer	67 (4.6)	66 (4.6)	1 (3.0)	.6635**	3 (2.5)	2 (2.2)	1 (3.3)	.7357**
Deep vein thrombosis (DVT)	11 (0.8)	11 (0.8)	0 (0.0)	.6123**	1 (0.8)	1 (1.1)	0 (0.0)	.5621**
Pulmonary embolism (PE)	12 (0.8)	12 (0.8)	0 (0.0)	.5964**	1 (0.8)	1 (1.1)	0 (0.0)	.5621**
Liver disease (any type)	35 (2.4)	35 (2.5)	0 (0.0)	.3620**	3 (2.5)	3 (3.3)	0 (0.0)	.3112**
Stroke	89 (6.1)	87 (6.1)	2 (6.1)	.9907**	13 (10.8)	11 (12.2)	2 (6.7)	.3965**

*T Test / ^ Wilcoxon rank sum test is used to calculate the *P*-value.

^^ Chi square/ ** Fisher's exact teat is used to calculate *P*-value.

*$ Nephrotoxic medications/material included IV Vancomycin, Gentamicin, Amikacin, Contrast, Colistin, Furosemide, and/or Sulfamethoxazole/trimethoprim.

55.6%; $P = .03$, respectively). However, Cox proportional hazards regression analysis did not show statistically significant differences between the two groups in terms of 30-day and in-hospital mortality (HR: 1.22; 95% CI: 0.7-2.12, $P = .48$ and HR: 1.07; 95% CI: 0.62-1.83, $P = .82$, respectively) (Table 2).

Complications During ICU Stay

Among the ESA group, statistically significantly higher odds of liver injury were observed than the control group (OR: 3.49; 95% CI: 1.03-11.81, $P = .04$). Moreover, patients who received ESA therapy also had higher odds of hospital-acquired infections (OR: 2.93; 95% CI: 1.03-8.33, $P = .04$). Other ICU complications were not statistically significant between the two groups (Table 3).

Discussion

In this multicenter retrospective cohort study, the impact of erythropoiesis-stimulating agents (ESA) on the clinical outcomes of critically ill patients with COVID-19 was examined. After propensity score matching for age, APACHE II score, chronic kidney disease, baseline serum creatinine, and hematocrit at admission, we found that using ESA was associated with longer lengths of stay in the ICU and hospital. This could be attributed to the development of liver injury (20.0% vs 6.7%) and the occurrence of acquired infections during the patient's stay.[27,28]

In contradiction to our findings, Benjamin et al reported four cases of anemic COVID-19 patients, two were critically ill, and all four patients received EPO analogs, changes from baseline hemoglobin and hematocrit were variable. However, it is good to note that the four patients were smokers in addition to one patient with CKD, which subsequently suggests possible ESA administration pre-COVID-19 infection. Most importantly, the length of ICU and hospital stay were variable (72 h, 8 weeks for non-ICU patients, and 22 days, 3 weeks for ICU patients). Hence, it is not possible to generalize the aforementioned results due to the small sample size, lack of comparable groups, and patients' baseline characteristics.[11] Moreover, in a

Table 2. The Outcomes of Critically ill Patients With COVID-19 After Propensity Score Matching.

	Number of outcomes/Total number of patients				
Outcomes	Control	ESA use	*P*-value	Hazard ratio (HR) (95%CI)	P-value $
30-day mortality, n (%)Δ	41 (50.6)	20 (71.4)	.06^^	1.22 (0.70, 2.12)	.48
In-hospital mortality, n (%)Δ	45 (55.6)	22 (78.6)	.03^^	1.07 (0.62, 1.83)	.82
				beta coefficient (estimates) (95%CI)	***P*-value** $*
Ventilator free days, median (Q1, Q3) Δ	0.0 (0.00, 24.00)	0.0 (0.00, 0.00)	.02^	−1.26 (−2.45, −0.07)	.04
ICU length of stay (days), median (Q1,Q3) Δ	10.0 (6.00, 17.00)	18.0 (10.00, 30.00)	<.01^	0.64 (0.31, 0.97)	<.01
Hospital length of stay (days), median (Q1,Q3) Δ	16.0 (11.00, 28.00)	20.0 (15.00, 31.00)	.06^	0.41 (0.12, 0.69)	<.01

ΔDenominator of the percentage is the total number of patients.
^ Wilcoxon rank sum test is used to calculate the *P*-value.
^^Chi-square test is used to calculate the *P*-value.
$Cox proportional hazards regression analysis used to calculate HR and *P*-value.
$*Generalized linear model is used to calculate estimates and *P*-value.

Table 3. The ICU Complications During Stay.

	Number of outcomes/Total number of patients				
Outcomes	Control	ESA use	*P*-value ^^	Odds ratio (OR) (95%CI)	*P*-value $*
New onset A fib., n(%)$	10/76 (11.6)	7/28 (25.0)	.08^^	2.53 (0.86, 7.46)	.09
Liver injury, n(%)Δ	6 (6.7)	6 (20.0)	.04**	3.49 (1.03, 11.81)	.04
All thrombosis cases, n(%)Δ	7 (7.8)	2 (6.7)	.84**	0.86 (0.17, 4.40)	.86
Hospital acquired infection, n(%)Δ	10 (11.1)	8 (26.7)	.04**	2.93 (1.03, 8.33)	.04

$Denominator of the percentage is patients who don't have atrial fibrillation as comorbidity.
ΔDenominator of the percentage is the total number of patients.
^^ Chi square/ ** Fisher's exact teat is used to calculate *P*-value.
$* Logistic regression is used to calculate the OR and *P*-value.

recent interventional study conducted by Samimagham et al, the mean hospital LOS was significantly less than that of control group ($P = .002$).[29] These results were inconsistent with our findings. It is worth mentioning that our cohort was comparable in terms of anemia variables and CKD at baseline.

Liu et al investigated 245 patients with COVID-19 and found a non-significant difference between all-cause mortality during hospitalization and baseline hemoglobin levels, and the OR of death with increasing serum hemoglobin level was 0.98 (95% CI: 0.96, 1.00, $P = .05$). Our findings came in line with this result; both 30-day mortality and in-hospital mortality were not statistically significant after PS matching ($P = .48$ and .82, respectively). The number of VFDs during the ICU stay was significantly shorter in the crude and regression analysis in the ESA group (beta coefficient (95% CI): −1.26 (−2.45-0.07), $P < .04$). Whereas, in a double-blind multicenter randomized control trial for 1302 critically ill patients, ESA therapy was found to reduce blood transfusion without any favorable effect on VFD, hospital stay, or mortality.[13]

There was a significant difference between the two groups' baseline albumin. Hypoalbuminemia has been prominent in the ESA group (mean26.3 (±5.84) in the ESA group vs 31.3 (±4.27) in the control group, $P = .0002$). A meta-analysis has reported that hypoalbuminemia in COVID-19 patients was found to be associated with a greater risk of hospital-acquired infections, higher viral load, and pronounced organ dysfunction in this group of patients.[30,31] he development of hypoalbuminemia in severe infectious diseases can be attributed to several factors, including increased capillary permeability, decreased protein synthesis, and elevated levels of pro-inflammatory cytokines in the bloodstream. These mechanisms contribute to the leakage of albumin from the blood vessels into the interstitial space, resulting in reduced levels of albumin in the blood.[32] In line with this, our study findings also showed significantly higher odds of hospital-acquired infections in the ESA group (P = .04). Moreover, our data shows that there were higher baseline blood glucose levels in both groups and a significant increase in the treatment group, which may be related to an increase in the risk for other hospital-acquired infections and increased hospital stay as well as mortality.

Based on the baseline data from the current cohort, it was observed that both groups had higher blood glucose levels at the baseline, with a significant increase in the ESA group, which may be related to an increase in the risk for other hospital-acquired infections and increased hospital stay as well as mortality. Hyperglycemia is one of the normal physiological responses for critically ill patients. Maintaining the blood glucose within the target ranges was found to significantly decrease mortality as well as morbidity in critically ill patients.[33] At the same time, hyperglycemia was found to decrease immune response and increase susceptibility to infection.[34]

Lastly, we found that the ESA group had a significantly higher incidence of liver injury. However, preclinical, and observational studies didn't report any instances of elevation in liver enzymes or acute liver injury due to ESA therapy, also the mechanism of ESA in causing liver injury is not well known.[35] However, we can attribute this to the low serum albumin in COVID-19 critically ill patients as discussed before which may contribute to end organ damage including hepatic dysfunction.

Our study had some limitations: First, some variables were not possibly to be controlled after PS matching such as albumin level, and blood glucose which might affect the external validity of the results. Second, having a small sample size and a short follow-up period may interpret study outcomes. Lastly, not being willing to assess inflammatory markers made it challenging to assess disease and outcome progression. In summary, our study is unique in the lack of well-controlled studies investigating the association between ESA administration in critically ill patients with COVID-19 in terms of clinical outcomes. Hence, controlled trials with larger sample sizes are warranted to illustrate a more pronounced correlation.

Conclusion

The use of ESAs in critically ill patients with COVID-19 was found to be associated with prolonged hospital and ICU stays. However, there were no observed survival benefits, and the use of ESAs was linked to lower ventilator-free days (VFDs). To validate these findings, it is recommended to conduct randomized controlled trials with larger sample sizes.

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Author Contributions

All authors contributed to data collection, analysis, drafted, revised, and approved the final version of the manuscript.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

The study was approved in January 2021 by King Abdullah International Medical Research Center (KAIMRC)–Institutional Review Board, Riyadh, Saudi Arabia (Ref.# NRC21R-004-01). Informed consent from the study patients was waived by KAIMRC due to the retrospective observational nature of the study. Participants' confidentiality was strictly observed throughout the study by using anonymous unique serial number for each subject and restricting data only to the investigators.

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ORCID iDs

Khalid Al Sulaiman https://orcid.org/0000-0002-5547-2043
Mai Alalawi https://orcid.org/0000-0002-3491-5685

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