

# Anaemia in Critically Ill COVID-19 Patients: A Cohort Study

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## Abstract

Anaemia is common in critically ill patients and has been shown to be a predictor of mortality in general Intensive Therapy Unit (ITU). Patients with Corona Virus Infectious Disease 2019 (CV-19) have also been reported to be anaemic, more profound in those admitted to ITU. We report our experience in the management of anaemic CV-19 patients admitted to ITU between 1st March and 1st June 2020. Demographic and clinical variables collected included age, sex, BMI, Charlson comorbidity index (CCI), Acute Physiology and Chronic Health Evaluation (APACHE) II score, haemoglobin concentration, blood transfusion, and mortality. 105 patients were admitted to the ITU with Severe Acute Respiratory Syndrome Coronavirus 2 disease requiring invasive mechanical ventilation and 73 patients with complete dataset were included in the study. Results: 36 patients (49%) were anaemic on admission, with 56 (77%) patients developing anaemia at some stage in the first 7 days of ITU stay. Anaemia at admission to ITU, a higher CCI and a higher APACHE II score were all independently associated with a blood transfusion (OR 12.5, 95% CI: 1.48 - 106,  $p = 0.02$ ), (OR 1.95, 95% CI: 1.08 - 3.52,  $p = 0.03$ ) and (OR 4.8, 95% CI: 1.48 - 15.6,  $p = 0.009$ ) respectively. Univariable analysis showed that an increasing age (OR 2.15, 95% CI: 1.18 - 3.91,  $p = 0.01$ ) and a higher APACHE II score (OR 1.60, 95% CI 1.01 - 2.54,  $p = 0.04$ ) were significantly associated with mortality. There was also some evidence of an association with mortality for CCI, although the results for this variable were only of borderline statistical significance. Neither haemoglobin concentration (OR 1.09, 95% CI: 0.83 - 1.43,  $p = 0.55$ ) or anaemia (OR 1.08, 95% CI: 0.41 - 2.85,  $p = 0.87$ ) at admission to ITU was significantly associated with mortality. 13 patients received blood transfusions, with a mean (SD) pretransfusion Hb of 75.2 (12.02). These numbers were too small to identify any association between receiving blood transfu-

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sion and mortality.

## Keywords

Anaemia, CV-19, SARS-CoV-2, Blood Transfusion, Mortality

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## 1. Introduction

Anaemia is common in critically ill patients and has been shown to be a predictor of mortality in general Intensive Therapy Unit (ITU) [1] [2]. Multiple factors contribute to anaemia including reduced red blood cell synthesis, increased destruction, loss from blood sampling, hemodilution, etc. The increased mortality stems from decreased oxygen carrying capacity and inability to meet tissue oxygen demand [3]. In septic shock, there is the added reduction in tissue oxygen utilization due to mitochondrial dysfunction [4].

Patients with Corona Virus Infectious Disease 2019 (CV-19) have also been reported to be anaemic, more profound in those admitted to ITU [5]. Systemic inflammation frequently leads to anaemia due to its effect on erythropoiesis [6]. Independent of this however, viruses are known to interfere with iron metabolism potentially leading to anaemia [5] [7]-[13]. Unlike in general ITU patients, the association between anaemia and severity of the disease or mortality in critically ill CV-19 patients is highly debated [5] [14] [15] [16] [17] [18]. Also, although the defining feature of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 ARDS) is severe hypoxemia leading to multiorgan failure, the etiological mechanisms are different to non-CV-19 ARDS. Septic shock is usually a complication [19]. The prognostic significance of anaemia in patients with CV-19 is thus not clear. The pathophysiology, management, and outcomes of CV-19 patients with anaemia thus warrant review. Our primary aim was to explore the prevalence of anaemia in critically ill SARS-CoV-2 patients. Analyses were also performed to examine association between anaemia and patient factors; age, sex, BMI, CCI, APACHE II score and Hb concentration (Hb) with blood transfusion and mortality.

## 2. Methods

### 2.1. Study Design

In this retrospective observational cohort study, all CV-19 Polymerase Chain Reaction (PCR) positive patients admitted to our ITU between 1st March 2020 and 1st June 2020 were included. Patients were excluded if PCR test was indeterminate, or a full set of data was not available. Patients were followed up until hospital discharge, transfer out to another Trust, or death. This study was a planned audit analysis of anonymised data collected via in-hospital informatics. Approval for the conduct of the study was obtained from the Trust R & D and ethics committee, and informed patient consent was waived.

## 2.2. Patient Characteristics

All patients in this study required invasive mechanical ventilation to treat severe hypoxia due to SARS-CoV-2 ARDS. All aspects of treatment were standardised as recommended by national guidelines [20]. Demographic and clinical variables collected included age, sex, BMI, CCI, APACHE II score, Hb, blood transfusion and mortality. Anaemia was defined as per WHO criteria [21]. CCI was used as an aggregate of chronic comorbidities and is a well validated tool to prognosticate mortality [22].

## 2.3. Statistical Analysis

The data analyses focused on factors associated with two outcomes: a transfusion within a week (yes/no) and mortality (alive/dead). Both univariable and multivariable analyses were performed. Categorical variables were summarised by the number and percentage in each category. Continuous variables were summarised by the mean and standard deviation if found to be normally distributed, and the median and inter-quartile range if not. The size of association between each patient factor and mortality were quantified by an odds ratio, presented along with corresponding confidence intervals. For the categorical variables, these represent the odds of mortality in patients with the characteristic, compared to those without. For the continuous variables, the odds ratios represent the relative change in the odds of mortality for a one-unit increase in each factor.

## 3. Results

1100 CV-19 PCR positive patients were treated in our hospital during this period. 105 patients were admitted to the ITU with SARS-CoV-2 ARDS requiring invasive mechanical ventilation. The original dataset included 88 patients. Data cleaning resulted in the removal of 15 patients (2 patients with indeterminate PCR test results, 2 with missing demographic data, 1 patient who received blood transfusion for bleeding, and 10 patients who were transferred out to another ITU, therefore were excluded as blood transfusion data were not available). A total of 73 patients with complete dataset were included in the study. 36 patients (49%) were anaemic on admission, with 56 (77%) developing anaemia at some stage in the first 7 days of ITU stay. Summaries of anaemia at admission, day 1 and over first 7 days of ITU admission and key demographic data of the patient group is provided in **Table 1**.

Anaemia at admission to ITU, a higher CCI and a higher APACHE II score were all independently associated with blood transfusion (OR 12.5, 95% CI: 1.48 - 106,  $p = 0.02$ ), (OR 1.95, 95% CI: 1.08 - 3.52,  $p = 0.03$ ) and (OR 4.8, 95% CI: 1.48 - 15.6,  $p = 0.009$ ) respectively. After adjusting for the two risk scores, the odds of a transfusion were 12 times higher for patients with anaemia, compared to those without. A one-unit increase in CCI was associated with a doubling of the odds of transfusion, whilst a 5-unit increase in APACHE II score was associated with the odds of a transfusion increasing over 3-fold. An increase in age and BMI;

**Table 1.** Summaries of anaemia and Haemoglobin.

Timepoint	Category	Females (n = 19)	Males (n = 54)	All Patients (n = 73)
<b>Anaemia</b>				
Admission	No anaemia	7 (37%)	30 (56%)	37 (51%)
	Anaemia	12 (63%)	24 (44%)	36 (49%)
Day 1	No anaemia	7 (37%)	25 (46%)	32 (44%)
	Anaemia	12 (63%)	29 (54%)	41 (56%)
Over first 7 days	No anaemia	4 (21%)	13 (24%)	17 (23%)
	Anaemia	15 (79%)	41 (76%)	56 (77%)
<b>Haemoglobin (g/l)</b>				
Admission	-	114.0 ± 20.3	120.5 ± 16.9	118.8 ± 17.9
Day 1	-	113.5 ± 20.4	117.9 ± 17.1	116.7 ± 18.0
Over first 7 days	-	102.7 ± 16.7	107.4 ± 15.4	106.2 ± 15.4

Summary statistics are n (%) or mean ± standard deviation.

and gender were not associated with increased chances of blood transfusion.

Univariable analysis showed increasing age (OR 2.15, 95% CI: 1.18 - 3.91,  $p = 0.01$ ) and higher APACHE II score (OR 1.60, 95% CI 1.01 - 2.54,  $p = 0.04$ ) were significantly associated with mortality. There was also some evidence of an association with mortality for CCI, although the results for this variable were only of borderline statistical significance. Every 10-year increase in age was associated with the risk of mortality increasing by a factor of 2.2. A 5-unit increase in APACHE II score was associated with a 60% increase in the odds of death. Multivariable results suggested that only age was found to be statistically significant. Increasing BMI; and gender were not associated with increased mortality.

Neither Hb concentration (OR 1.09, 95% CI: 0.83 - 1.43,  $p = 0.55$ ) or anaemia (OR 1.08, 95% CI: 0.41 - 2.85,  $p = 0.87$ ) at admission to ITU were significantly associated with mortality. 13 patients received blood transfusions, with a mean (SD) pretransfusion Hb of 75.2 g/l (12.02). These numbers were too small to identify any association between receiving blood transfusion and mortality.

Associations between patient / baseline factors and transfusion within 1 week are shown in **Table 2** and **Table 3**. Associations between patient/baseline factors and death are shown in **Table 4**.

## 4. Discussion

The World Health Organisation defines anaemia as an Hb < 120 g/l in women

**Table 2.** Associations between patient/baseline factors and transfusion within 1 week.

Factor	Summary		Association	
	No transfusion	Transfusion	OR (95% CI)	P-value
Age (Years) <sup>(**)</sup>	56.9 ± 9.7	62.1 ± 7.1	1.87 (0.94, 3.75)	0.08
BMI <sup>(*)</sup>	31.9 ± 7.2	31.0 ± 6.0	0.90 (0.56, 1.45)	0.67
Gender				
Female	15 (79%)	4 (21%)	1	0.67
Male	45 (83%)	9 (17%)	0.75 (0.20, 2.79)	
Charlson comorbidity index	2 [1, 2]	3 [2, 4]	2.11 (1.29, 3.46)	0.003
APACHE II score <sup>(*)</sup>	14.7 ± 5.0	22.2 ± 6.4	3.87 (1.78, 8.40)	0.001
Haemoglobin at admission (g/l) <sup>(**)</sup>	123 ± 16	100 ± 16	0.40 (0.23, 0.67)	0.001
Anaemia at admission.				
No	35 (95%)	2 (5%)	1	
Yes	25 (69%)	11 (31%)	7.70 (1.57, 37.8)	0.01

Summary statistics are mean ± standard deviation, median [inter-quartile range] or number (percentage). (\*) Odds ratio reported for 5-unit increase in variable. (\*\*) Odds ratio reported for 10-unit increase in variable.

**Table 3.** Associations between patient/baseline factors and transfusion within 1 week: Multivariable analysis.

Factor	Odds Ratio (95% CI)	P-value
Charlson comorbidity index	1.95 (1.08, 3.52)	0.03
APACHE II score <sup>(*)</sup>	4.80 (1.48, 15.6)	0.009
Anaemia at admission No	1	
Yes	12.5 (1.48, 106)	0.02

(\*) Odds ratio reported for 5-unit increase in variable.

and < 130 g/l in men [21]. Two large studies reported its prevalence between 60% - 70% on admission to ITU with a mean (SD) pre-transfusion Hb of 84 (13) g/l and 86 (17) g/l [1] [2]. There are multiple reasons contributing to the development of anaemia in these patients and are characterised by anaemia of inflammation and functional iron deficiency [6] [14]. A nadir Hb < 90 g/l was shown to be a predictor of mortality in general ITU patients [2]. The 90-day mortality in patients who were mechanically ventilated for acute respiratory

**Table 4.** Associations between patient/baseline factors and death.

Factor	Summary		Association	
	Alive	Dead	OR (95% CI)	P-value
Age (Years) <sup>(**)</sup>	53.8 ± 8.3	59.9 ± 9.4	2.15 (1.18, 3.91)	0.01
BMI <sup>(*)</sup>	31.5 ± 5.2	31.8 ± 7.8	1.03 (0.72, 1.48)	0.85
Gender				
Female	9 (47%)	10 (53%)	1	0.17
Male	16 (30%)	38 (70%)	2.14 (0.73, 6.25)	
Charlson comorbidity index	2 [1, 2]	2 [1, 3]	1.52 (0.99, 2.33)	0.06
APACHE II score <sup>(*)</sup>	14.0 ± 5.8	17.1 ± 5.9	1.60 (1.01, 2.54)	0.04
Haemoglobin at admission (g/l) <sup>(**)</sup>	117 ± 17	120 ± 18	1.09 (0.83, 1.43)	0.55
Anaemia at admission.				
No	13 (35%)	24 (65%)	1	
Yes	12 (33%)	24 (67%)	1.08 (0.41, 2.85)	0.87

Summary statistics are mean ± standard deviation, median [inter-quartile range] or number (percentage). (\*) Odds ratio reported for 5-unit increase in variable. (\*\*) Odds ratio reported for 10-unit increase in variable.

failure was 57.1% in anaemic compared to 25% in non-anaemic patients [23]. Whether it is the reduced oxygen carrying capacity and delivery seen in patients with cardiorespiratory failure and or reduced oxygen utilization which is the hallmark of septic shock, anaemia can only further worsen tissue hypoxia leading to multiorgan failure and death [3] [4].

This study highlights that anaemia is a significant factor in critically ill CV-19 patients with around 50% anaemic on admission to ITU and 77% developing it by the end of the first week. Patients with increasing burden of pre-existing comorbidities and disease severity are at a higher risk of being anaemic and requiring blood transfusion. Increasing age and disease severity are linked to higher mortality.

This study however did not show an association between anaemia and increased mortality. The prognostic significance of anaemia in patients with CV-19 is not clear. That anaemia is common in critically ill CV-19 patients and that it predicts mortality has been reported by multiple authors [14] [15] [16] [17]. Many of these studies had several limitations including regional variations, study design, patient selection and sample size. Bellmann-Weiler *et al.* (2020) in their retrospective analysis of 259 patients reported that anaemia was associated with increased in-hospital mortality but not with admission to ITU or need for

mechanical ventilation [14]. Oh *et al.* (2021) reported that moderate to severe anaemia was independently associated with death. This was a single centre retrospective study of a randomly selected set of 750 patients [17]. The results of our study are similar to the findings from other authors [5] [18]. Cecconi *et al.* (2020) did not find Hb to be a predictor of death in their cohort of 239 CV-19 patients [18]. However, the mean Hb (SD) in our study was 118.8 g/dl (17.9) compared to theirs 13.9 g/dl (1.88). A recent meta-analysis involving 55,563 CV-19 patients reported lower Hb, more profound in those with severe compared to moderate disease and in those admitted to ITU [5]. The authors did not find a significant difference in mean Hb levels between survivors and non-survivors. They recommended prospective studies to understand the impact of anaemia on mortality in CV-19 patients. The authors reported higher mean serum ferritin levels in severe compared to moderate CV-19 cases [WMD, 473.25 ng/mL (95% CI 382.52; 563.98)] and non-survivors compared to survivors [606.37 ng/mL (95% CI 461.86; 750.88)]. Also, a lower red blood cell count and higher red cell distribution width were seen in severe compared to moderate cases. A ferritin/transferrin ratio >10 was shown to be predictor for ITU admission and the need for mechanical ventilation [14]. A compensatory increase in serum ferritin to sequester iron intracellularly and thus limit its availability to pathogens has been described as the body's innate response to limit viral replication [7], but it is also a marker of severity of inflammation due to its role in cytokine release [24].

The defining feature of SARS-CoV-2 ARDS is severe hypoxemia leading to multiorgan failure, septic shock is usually a complication [19]. The etiopathological mechanisms are different to non-CV-19 ARDS. There is an increasing understanding that the mechanism of profound hypoxemia is unlike non-CV-19 ARDS; with a greater emphasis on diffuse vascular endothelial dysfunction: abolition of hypoxic pulmonary vasoconstriction, endothelial inflammation, and pulmonary thrombosis, all leading to V/Q mismatching and severe hypoxia [8] [25] [26] [27]. Lung compliance and lung volumes are usually preserved [26]. Also, viruses are known to interfere with iron metabolism. Many viruses obtain entry into host cells by interacting with the transferrin receptor, the gatekeeper of iron metabolism [9]. Viruses require an optimal level of iron within host cells for its replication [10] [11]. In critical illness, an iron restricted erythropoiesis by reducing the bioavailability and alterations in iron and haemoglobin metabolism have been reported [5] [7] [8] [9] [11] all of which can lead to anaemia [9]. Reducing the bioavailability through activation of hormone hepcidin has been described as the body's innate immune response to deprive pathogens of iron [7]. A number of studies have reported CV-19 induced autoimmune haemolytic anaemia [12] [13] [17].

## 5. Conclusion

Anaemia imposes a significant burden on critically ill patient including those

with CV-19. However, its prognostic significance is not clear. It is evident that there are multiple confounding factors that may prevent using anaemia as a predictor of poor outcomes in critically ill CV-19 patients. Despite its limitations, this study contributes to a body of evidence supporting the need for prospective well conducted studies to understand the impact of anaemia on mortality in CV-19 patients.

## 6. Limitations

This was a single centre, retrospective, observational study with a small number of patients. Association of mortality with other biochemical markers of severity of illness like ferritin, d-dimer, lactate dehydrogenase and differentiating acute from chronic anaemia were not taken into consideration. At the start of the pandemic, the significance of these parameters was not well understood and hence was not studied consistently.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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