The Association between Anemia and Mortality of Severe Pneumonia COVID-19 Patients in the High Care Unit of a Tertiary Hospital in Jakarta

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ABSTRACT

Background: Numerous studies explored the association between anemia and mortality in patients with severe pneumonia due to COVID-19. However, the findings were inconsistent. Therefore, this study was conducted to investigate the association between anemia at HCU admission and in-hospital mortality in severe pneumonia COVID-19 patients. Methods: This retrospective cohort study obtained data on 110 COVID-19 patients with severe pneumonia who were admitted to the HCU between January, 1st 2021, and May 31st, 2021. Patients were categorized as anemic and non-anemic based on the World Health Organization (WHO) guidelines. The demographic and clinical characteristics of the subjects were described. The Chi-squared test was carried out followed by a logistic regression test to determine the association of anemia and mortality. Results: Anemia was observed in 31% of 110 patients with severe pneumonia COVID-19. The source population consisted of 60.9% men and 39.1% women with a median age of 58 years. The most prevalent comorbidity was hypertension (38.2%), followed by diabetes mellitus (27.2%), renal diseases (19.1%) and heart diseases (10%). TAnemia on HCU admission was associated with in-hospital mortality in patients with severe pneumonia COVID-19 (RR: 2.794, 95% CI 1.470-5.312). After adjusting comorbidities as confounding factors, anemia was independently associated with mortality (RR: 2.204, 95% CI: 1.124-4.323, P < 0.021). The result also showed anemic patients had longer lengths of stay and higher levels of D-dimer than non-anemic patients. The median duration length of stay among the anemic and non-anemic was 16 (11-22) and 13 (9-17) days, respectively. The median D-dimer among the anemic and non-anemic was 2220 µg/ml and 1010 µg/ml, respectively. Conclusion: There is a significant association between anemia at HCU admission and mortality in patients with severe pneumonia COVID-19 during hospitalization.

Keywords: Anemia, Mortality, Severe Pneumonia COVID-19, Retrospective Cohort.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a recently emerged novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which has rapidly become a global health concern.[1] The most common symptoms at onset include fever, fatigue, dry cough, myalgia, and dyspnea. While headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting are less common symptoms.[2] Most of COVID-19 patients have mild symptoms. According to Shang Y et al., there were 14% of patients developed into severe cases, and 5% became critically ill with a mortality rate of 2.3-3.83% mortality.[3] Patients with mild symptoms are treated at home and self-isolated, while those who suffer from severe pneumonia and are critically ill require hospitalization or admitted to the intensive care unit.[4] Severe cases are diagnosed by SpO_2 less than 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) less than 300 mm Hg, respiratory rate more than 30 breaths/min, and/ or lung infiltrates more than 50%. Patients with respiratory failure, septic shock, and/or multiple organ dysfunction are categorized as critically ill.[5]

Anemia is defined by WHO as hemoglobin (Hb) levels less than 12.0 g/dL in women, and less than 13.0 g/dL in men. The low level of hemoglobin describes a condition where the number of red blood cells and their oxygen-carrying capacity are insufficient to meet the body's physiologic needs.[6] Hemoglobin acts as a carrier of oxygen (O_2) in the lungs and releases it to various tissue organs. Hemoglobin also plays an important role in maintaining blood oxygen balance and partial pressure (PaO2) levels. Specific physiology varies in every individual, and the most common cause of anemia is nutritional deficiencies. Other causes include acute and chronic inflammation, parasitic infections, as well as inherited or acquired disorders affecting hemoglobin synthesis.[6,7]

Pneumonia in COVID-19 causes lung injury, leading to a decline in the oxygen levels resulting in a decline of oxygen level in the blood, which makes the oxygen supply to tissues become limited. Low Hb levels reduce the ability of blood to deliver oxygen, thereby worsening the disease. As a result, anemia is deemed to increase mortality in severe pneumonia COVID-19.[7]

Previous studies investigated the association between anemia and COVID-19, but the results were inconsistent. Several studies in various countries reported that COVID-19 patients with anemia are at higher risk of developing severe pneumonia infection and higher risk of mortality.[8,9] However, this finding contradicts the findings of a study in Italy, which found that anemia often occurs in the viral infection but is not directly associated with mortality.[3] Cecconi, et al. also reported that there was no significant association between Hb levels and survival of COVID-19 patients.[10] Therefore, this study aimed to determine the association between anemia and mortality of patients with severe pneumonia COVID-19 who were treated at the HCU of the tertiary facility, Dr. Cipto Mangunkusumo General Hospital, which serves as a national referral hospital in Jakarta, Indonesia. Even though right now COVID-19 is not a pandemic disease anymore, as clinicians we will meet COVID-19 as sporadic cases in clinical practice.

METHODS

A retrospective cohort study was conducted on all patients diagnosed with severe pneumonia and COVID-19 who met the eligibility criteria. at HCU KIARA Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia between January 1st, 2021, and May 31st, 2021 We enrolled 110 COVID-19 patients with severe pneumonia who were admitted high care unit at the hospital. We categorized the patients into two groups based on their Hb levels on admission. Anemia was defined based on WHO guidelines where normal levels for men and women are >13g/dL and >12g/dL, respectively.

This study collected data from electronic medical records (EHR) using the total sample method, which was subsequently reviewed by the Department of Internal Medicine at the study site. which were then analyzed by the Department of Internal Medicine at the study site. This study protocol was reviewed and approved by the ethical committee in the Faculty of Medicine

Universitas Indonesia, approval number KET-667/UN2.F1/ETIK/PPM.00.02/2022. The inclusion criteria were patients over the age of 18, who were admitted to HCU Kiara, underwent a laboratory examination including Hb levels, and positive results of Polymerase Chain Reaction (PCR) swab examination. The exclusion criterion is no data on the date of death.

The demographic and characteristics of patients' data variables are presented in either frequency and percentage or median and interquartile range. Statistical analysis was carried out with Chi-square to determine the association between anemia and in-hospital mortality followed by logistic regression to adjust the confounding factors. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Mac version 26.0 tool. P-values of < 0.05 were regarded as statistically significant.

RESULTS

A total of 34 out of 110 patients with severe pneumonia COVID-19 who were admitted to HCU at the study hospital were anemic, accounting for 31% of the sample population.

The study participants were categorized into two groups for comparison based on the Hb cut-off, as shown in **Table 1** and **2**. **Table 1** shows the demographic and clinical characteristics of the patients with a median age of 58 years (interquartile range 47.75-66). The samples consisted of 67 (60.9 %) men and 43 (39.1 %) women. The most common comorbidity in this study was hypertension (38.2%), followed by diabetes mellitus (27.3 %) renal disease (19.1%), and heart disease (10 %).

Patients with anemia on admission had a higher length of stay, with a median duration of 16 (11-22) days in anemic patients and 13 (9-17) days for non-anemic patients, respectively.

Table 2 describes the laboratory findings of severe pneumonia COVID-19 patients. The total median Hb was 13.7 with a range of 12.0-14.8, while non-anemic and anemic patients had values of 14.4 and 10.7, respectively. Furthermore, all of the samples demonstrated high CRP levels, where the non-anemic and anemic groups had 93.0 and 61.1, respectively with a median of 80.7 mg/dl. At the time of admission, the median D-dimer of 110 patients was 1220 μg/ml, with non-anemic patients having values of 1010g/ml and anemic patients having values of 2220g/ml.

Table 1. The Demographic and Clinical Characteristics of Study Participants.

Patients' Characteristic	Total (n=110)	Non-anemia (n=76)	Anemia (n=34)
Age, (median, IQR)	58 (47.75-66)	58 (51-65.75)	57.50 (34.75-68.50)
Gender			
Male n, (%)	67 (60.9)	45 (59.2)	22 (64.7)
Female n, (%)	43 (39.1)	31 (40.8)	12 (35.3)
Comorbidity			
Hypertension n, (%)	42 (38.2)	30 (39.5)	12 (35.3)
Diabetes Mellitus n, (%)	30 (27.3)	24 (31.6)	6 (17.6)
Renal Disease n, (%)	21 (19.1)	15 (19.7)	6 (17.6)
Heart Disease n, (%)	11 (10)	4 (5.3)	7 (20.6)
Others n, (%)	39 (35.5)	27 (35.5)	12 (35.3)
No Comorbidity n, (%)	1 (0.9)	1 (1.3)	
Length of stay (median, IQR)	14 (10-18)	13 (9-17)	16 (11-22)
Initial Oxygen Therapy n, %			
Nasal Cannula	13 (11.8)	6 (7.9)	7 (20.6)
Simple mask	13 (11.8)	8 (10.5)	5 (14.7)
Non-rebreathing mask	31 (28.2)	22 (28.9)	9 (26.5)
Non-invasive ventilation	49 (44.5)	36 (47.4)	13 (38.2)
Intubation	4 (3.6)	4 (5.3)	
Antiviral therapy			
Remdesivir, n (%)	78 (70.9)	57 (75)	21 (61.8)
Favipiravir, n (%)	9 (8.2)	7 (9.2)	2 (5.9)
Oseltamivir,n (%)	7 (6.4)	4 (5.3)	3 (8.8)
No antiviral therapy, n (%)	16 (14.5)	8 (10.5)	8 (23.5)

Table 2. Laboratory findings of severe pneumonia COVID-19 patients in the HCU

Laboratory Findings	Total (n=110)	Non-anemia (n=76)	Anemia (n=34)
Haemoglobin(median,IQR)	13.7 (12.0-14.8)	14.4 (13.7-15.40)	10.7 (8.53-11.9)
White blood cells (median, IQR)	9085 (6355-12162)	8760 (6057-10727)	10730 (6417-13375)
Trombosit (median,IQR)	227500 (169750-284250)	225000 (171000-267000)	239500 (157500-308750)
CRP (median, mg/dl, IQR)	80.7 (35.525-149.100)	93.0 (40.300-161.525)	61.1 (13.125-116.700)
D-Dimer (median, µg/ml, IQR)	1220 (565-2777.50)	1010 (480-1965)	2220 (847.5-3825)

The results found that 15 out of 34 (44.1%) anemic inpatients died. **Table 3** shows that anemia is a significant risk factor for death due to severe pneumonia in COVID-19 patients. Furthermore, there was a significant association between anemia and mortality during hospitalization of severe pneumonia COVID-19 patients in men and women (RR: 2.794, 95% CI 1.470-5.312, p = 0.001).

We performed logistic regression analysis to adjust the results of bivariate analysis by adding confounding variables, and we established an independent association between anemia on HCU admission and in-hospital mortality in COVID-19 patients with severe pneumonia, that were hypertension, diabetes mellitus, kidney disease, heart disease using regression analysis anemia was independently had an association with mortality (RR: 2.204, 95% CI: 1.124-4.323, p = 0.021).

DISCUSSION

We found that anemia on HCU admission in patients with severe pneumonia COVID-19 is independently associated with a higher risk of in-hospital mortality. This condition has been observed in critically ill patients, but knowledge regarding its relationship with the viral infection is still lacking.[11] This study was carried out among 110 severe COVID-19 inpatients treated at the HCU with a median age of 58 years (IQR: 47.75-66 years), of which 60.9% and 39.1% were men and women, respectively. A total of 34 anemic and 76 non-anemic inpatients were found, namely 31% and 69% of the population, respectively.

Furthermore, more than half of the patients had more than one comorbidity, with hypertension being the most common in 38.2%, followed by diabetes mellitus, kidney disease, and heart disease in 27.3%, 19.1%, and 10%, respectively.

Table 3. The bivariate analysis between anemia and in-hospital mortality in patients with severe pneumonia COVID-19.

Anemia Status	Alive n, %	Dead n, %	RR (CI 95%)	p
Non-anemia	64 (84.2)	12 (15.8)	2.794 (1.470-5.312)	0.001
Anemia	19 (55.9)	15 (44.1)		

Table 4. The logistic regression analysis of anemia and mortality, as adjusted by confounding variables.

	RR (CI 95%)	p
Crude RR : Anemia	2.794 (1.470-5.312)	0.001
Adjusted		
+ Hypertension	2.654 (1.406-5.009)	0.003
+ Diabetes Mellitus	2.539 (1.329-4.854)	0.005
+ Kidney Disease	2.356 (1.201-4.621)	0.013
+ Heart	2.427 (1.248-4.724)	0.009
+ Others	2.204 (1.124-4.323)	0.021

This finding is consistent with Tao, et al. where these conditions were comorbid for severe pneumonia COVID19.[8] Starke, et al. carried out a meta-analysis of seventy studies, which showed that increasing age as well as comorbidities were related to disease severity, but the mechanism was still unclear.[12]

Patients with anemia on admission had a longer length of stay. This study also assessed anemic or non-anemic patients based on their Hb levels using the WHO guidelines, with a median duration of hospitalization of 16 (11-22) days and 13 (9-17) days, respectively. This finding is in line with a study conducted by Mi Oh, et al., which reported that patients with anemia on admission had a longer duration.[11]

Coagulation disorders, such as disseminated intravascular coagulation (DIC), are often found in severe COVID-19 infections. Anemia was associated with coagulation variables because anemic patients have higher D-dimer levers compared to others.[13] Based on a study in Wuhan, China, the condition was an independent risk factor associated with severe COVID-19, and CRP as well as D-dimer levels were significantly higher in affected people.[8] Furthermore, D-dimer is a fibrin degradation product, which is often used to diagnose thrombosis disorder, and its levels at admission increase along with the severity of community-acquired pneumonia (CAP).[14] The majority of patients in this study had high levels above 500 g/ml, with medians of 1010 g/ml and 2220 g/ml in the non-anemic and anemic groups, respectively. These results are consistent with findings of the study conducted by Helin, et al., which showed that anemic patients had higher levels of D-dimer.[13]

Anemia is common among severely ill patients due to inflammation, and it has been reported to aggravate the severity of the underlying disease and is related to poor outcomes as well as mortality in COVID-19 patients. Previous studies also revealed that it can worsen with age and the presence of comorbidities.[8] In another observational study among 206 patients, anemia was a common manifestation of COVID-19 but had no direct association with mortality.[15] In this study, a statistically significant association was found between the condition of anemia and death during hospitalization of patients with severe pneumonia COVID-19 (P = 0.001). This finding is consistent with Zhou, et al., which also obtained a similar significant association (P = 0.0094). Furthermore, this is in line with another study in Iran where the frequency of death, ICU admission, and need for ventilators were significantly higher in anemic patients compared to others.[9] Most of the COVID-19 infections associated with anemia are caused by an inflammatory process, which is characterized by elevated or normal serum ferritin. In the majority of cases, it is also indicated by decreased transferrin saturation as well as increased inflammatory indicators, such as erythrocyte sedimentation rate (ESR) and CRP .[15]

CONCLUSION

The proportion of anemia in patients with severe pneumonia COVID-19 in the HCU was 31%. Furthermore, 15 of 34 anemic patients died during hospitalization, and they accounted for 44.1% of the sample population. This study found a significant association between anemia on HCU admission and in-hospital mortality in COVID-19 patients with severe pneumonia. As a clinician, if we find sporadic severe COVID-19 patients in the HCU who experience anemia, then the clinician should correct the Hb level immediately to the normal range.

DATA AVAILABILITY STATEMENT

The data used to support the findings are available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

FUNDING SOURCES

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