Original Article

Relationship of anemia with COVID-19 deaths: A retrospective cross-sectional study

Manish Jha, M.L. Tak, Rashmi Gupta, Priyamvada Sharma, Vikas Rajpurohit, Prachi Mathur, Nayanika Gaur[1]

Department of Anesthesia, Dr. S. N. Medical College and Associated Hospitals, Jodhpur, Rajasthan, [1]Department of Obstetrics and Gynecology, Kirti IVF Clinic, Jodhpur, Rajasthan, India

Abstract

Background and Aims: With the second wave of COVID-19, India lost close to three lakh people within the span of a few months. In this study, we aimed to investigate the impact of anemia on the severity of COVID-19 based on the hemoglobin (Hb) concentration of the patients noted at the time of admission to the intensive care unit (ICU), to mark Hb as a prognostic marker of disease severity for the future.

Material and Methods: Retrospective data was collected from 784 patients admitted to the COVID adult ICU between March and June 2021. Patients were identified as anemic and non-anemic based on the World Health Organization (WHO) guidelines. Chi-squared test was applied to see the relationship of anemia with the patient deaths.

Results: Among the 784 patients, 507 succumbed to COVID-19. Of these, 49.3% had varying degrees of anemia. Significant correlation of anemia with death due to COVID-19 was found in males and females ($P = 0.002106$ and $P = 0.033071$, respectively) and in patients without any other comorbidities except anemia ($P = 0.002020$). This suggests that anemia is independently an important parameter that plays a role in severity of COVID-19.

Conclusion: Upon observing a significant correlation between anemia and COVID-19 severity, it can be stated that anemia should be considered as an independent prognostic risk factor for COVID-19 and that hemoglobin can be used for risk stratification in patients under home or hospital care.

Keywords: Anemia, comorbidities with Covid-19, Covid-19 mortality, Covid-19, hemoglobin estimation, intensive care unit care

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly evolved into a global pandemic with over 160 million confirmed cases worldwide and total deaths officially exceeding 3.3 million[1] as of May 2021, with United States of America and India having the greatest number of COVID-19-related deaths.

COVID-19 infection is considered severe when there is a need for intensive care unit (ICU) admission and/or mechanical ventilation, or death due to the disease.[2] About 5%–10% of COVID-19 patients require hospital admissions.[3] The World Health Organization (WHO) has listed risk factors that increases the severity of COVID-19 infection. These risk factors are obesity, smoking, alcohol, physical inactivity, pollution, diabetes, cardiovascular disease, respiratory disease, and cancer.[4] The Centers for Disease Control and Prevention (CDC) summarizes comorbidities that have significant association with increasing risk of severe COVID-19 illness, namely, cancer, cerebrovascular disease,

Address for correspondence: Dr. Nayanika Gaur, B-4, Shastri Nagar, Jodhpur - 342 003, Rajasthan, India.
E-mail: nayanika.gaur@gmail.com

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_63_22

How to cite this article: Jha M, Tak ML, Gupta R, Sharma P, Rajpurohit V, Mathur P, *et al*. Relationship of anemia with COVID-19 deaths: A retrospective cross-sectional study. J Anaesthesiol Clin Pharmacol 2022;38:S115-9.

Submitted: 14-Feb-2022 **Revised:** 09-Apr-2022
Accepted: 10-Apr-2022 **Published:** 15-Jun-2022

chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus type 1 and type 2, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), obesity (BMI ≥30 kg/m^2), pregnancy, and smoking (current and former).[5] While both groups have listed almost similar risk factors, there is some literature with mixed evidence about the correlation of anemia with the risk of severity of COVID-19. All the published data available for reference in which the correlation of anemia with COVID-19 is studied have not removed the biases of other comorbidities within their data, thereby giving mixed results. Also, there are no significant data on the relationship of anemia with COVID-19 generated from India. Several tests have been attempted to stratify the risks in COVID-19 infection. Studies have demonstrated the use of neutrophil-to-lymphocyte ratio (NLR) as one such tool.[6] However, it is simply a marker of inflammation in general. In our study, we aimed to observe the trends of disease progression in patients who succumbed to COVID-19 without any other comorbidity except anemia and compared whether anemia was in anyway a marker of worsening of COVID-19. We believe that anemia in a COVID-19 infected person could have an impact on the severity of the disease as well. With this hypothesis, we analyzed the ICU admissions of COVID-19 that occurred in hospitals attached to Dr. S. N. Medical College, Jodhpur, with the sole purpose to prevent the severity of the disease with one modifiable risk factor, anemia, in the forthcoming COVID-19 waves.

Material and Methods

A cross-sectional, retrospective data analysis of all of the patients admitted to the ICU of MDM and MGH hospital, Jodhpur, from 1 March 2021 to 1 June 2021 due to severe COVID-19 infection was carried out. The data was collected manually and analyzed by the Department of Anesthesia and Critical Care, Dr. S. N. Medical College, Jodhpur. Ethical approval was taken from the institutional ethical committee (SNMC/IEC/IIP/2021/022).

All laboratory-confirmed COVID-19 patients including those who succumbed to the disease were included in the analysis. All pregnant patients with COVID-19 infection, patients ≥65 years and <18 years of age were marked as exclusion criteria for the study group. Comorbidities as per CDC guidelines, that is, cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus type 1 and type 2, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), and smoking (current and former), were included and marked as known risk factors for COVID-19 severity.

From a total of 906 patients admitted to the ICU for severe COVID-19 infection, we used the arbitrary cutoffs of hemoglobin (Hb) values on admission as per the WHO guidelines where normal hemoglobin concentration in males and females is defined as >13 g/dl and >12 g/dl, respectively. Mild anemia is defined as a Hb concentration of 11–12.9 g/dl in males and 11–11.9 g/dl in females. Moderate anemia is within the range of 8–10.9 g/dl in both males and females, and severe anemia is when hemoglobin concentration is <8 g/dl in both males and females. After excluding the patients based on the exclusion criteria, the remaining 784 patients who matched our inclusion criteria were divided into males, females, anemic (into separate categories as per abovementioned WHO criteria), and non-anemic groups. The collected data contained baseline demographics, clinical comorbidities, laboratory values of hemoglobin, duration of symptoms, and duration of hospital stay.

Our primary outcome was a composite endpoint of severe COVID-19 outcomes among the different anemia cohorts. We defined the composite endpoint as death during hospitalization. The data was analyzed on the basis of the trends of COVID-19-related deaths in patients with and without anemia, and comparing the presence or absence of anemia in those who survived or succumbed to COVID-19 during their ICU stay. Variations in the trends were analyzed among the ages, gender, and rural and urban populations. The trends were quantified on the basis of the duration of hospital stay where correlation of worsening of the disease with respect to anemia were observed and duration of symptomatic days where trends of duration of symptoms with respect to anemia were observed.

Statistical analysis was performed using the IBM SPSS 25.0 software. The frequency distribution and descriptive statistics were calculated for categorical and quantitative data, respectively. Descriptive analysis was performed to characterize the study population.

The level of anemia was compared with the patients who succumbed to COVID-19 using contingency tables. Chi-square test was applied to see the relationship of anemia with the deaths of patients who were admitted to the ICU with a confirmed COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test. Kaplan–Meier estimate was used to estimate survival and Logrank (Mantel–Cox) test was used to compare the age of survival for different categories. Level of significance was taken as 0.05 such that, P value less than 0.05 represented significance of the result. We also calculated the means with standard deviations for symptomatic days and days of hospitalization in the study cohort.

Results

A total of 906 patients were considered for the study. Of those, 122 patients were excluded based on our exclusion criteria (pregnant patients and those of >65 years or <18 years of age). Of the remaining 784 patients, 300 were females and 484 were males. A total 277 patients were discharged alive while 507 succumbed to COVID-19. Within our study population, 441 patients did not have anemia (mild, moderate, or severe) while the remaining 343 had varying degrees of anemia. Five hundred fifty-one of 784 patients (70.28%) had no another comorbidity (except anemia) while 233 of 784 patients (29.71%) had other comorbidities too (as per CDC guidelines, that are marked as known risk factors for COVID-19 severity).

Overall results of the analysis ($n = 784$) suggest a significant correlation of anemia with the severity of COVID-19, that is death in the study population ($P = 0.000204$). Similarly, a significant correlation of anemia with the death in patient suffering from COVID-19 was found in both subgroups, male and female, with $P = 0.002106$ and $P = 0.033071$, respectively, as shown in Table 1. In another subgroup of patients without any other comorbidities except anemia ($n = 551$), significant correlation of anemia with death due to COVID-19 ($P = 0.002020$) was found. This suggests that anemia is independently an important parameter that plays a role in severity of COVID-19. Within the subgroups of male and female (without comorbidities except anemia), anemic males showed significantly increased deaths ($P = 0.003930$). However, in the subgroup of females without comorbidities except anemia, the data was insignificant. That can be attributed to the variations in the number of females in the analyzed data as shown in Table 2.

Overall, the mean age of survival in males and females (irrespective of comorbidities) was 56.96 and 56.01 years, respectively. Combined (male and female) mean age of survival was found to be 56.54 years while in patients without anemia (irrespective of another comorbidity), it was 59.20 years, which is statistically significant ($P = 0.029$). In patients without any comorbidities except anemia, mean age of survival was 56.13 years while in those without anemia, it was 59.32 years. However, this result is statistically significant only in the subgroup of female population (without comorbidities) included in the analysis (55.12 years with anemia versus 61.52 years without anemia ($P = 0.037$)) and this was analyzed using Kaplan–Meier estimate.

We tried to relate the duration of symptoms and duration of hospitalization as a count for the morbidity pertaining to COVID-19. Overall, patients who survived severe COVID-19 infection had a mean of 14.7 ± 7.92 symptomatic days and 9.73 ± 7.40 days of hospitalization. While the ones who succumbed to the disease had a mean of 13.07 ± 9.01 symptomatic days and 7.44 ± 6.80 days of hospitalization.

Discussion

Our cross-sectional, retrospective study of 784 patients admitted with COVID-19 in Jodhpur, Rajasthan showed that anemia on admission was an independent risk factor for COVID-19 infection and that it was predictive of the severity

Table 1: Significance of anemia as a risk factor for death due to COVID-19 in the overall collected data

Anemia level	Alive		Dead		Chi-squared test, *P*
	Count	%	Count	%	
Combined					
Normal	184	41.7%	257	58.3%	19.613753, 0.000204
Mild Anemia	55	30.1%	128	69.9%	
Moderate Anemia	33	24.3%	103	75.7%	
Severe Anemia	5	20.8%	19	79.2%	
Gender					
Female					
Normal	49	36.6%	85	63.4%	8.732265, 0.033071
Mild Anemia	25	37.9%	41	62.1%	
Moderate Anemia	20	22.5%	69	77.5%	
Severe Anemia	1	9.1%	10	90.9%	
Male					
Normal	135	44.0%	172	56.0%	14.685222, 0.002106
Mild anemia	30	25.6%	87	74.4%	
Moderate Anemia	13	27.7%	34	72.3%	
Severe Anemia	4	30.8%	9	69.2%	

Table 2: Significance of anemia as a risk factor for death due to COVID-19 in patients with no other comorbidity except anemia

Anemia level	Alive		Dead		Chi-squared test, *P*
	Count	%	Count	%	
Combined					
Normal	136	42.2%	186	57.8%	14.774509, 0.002020
Mild anemia	38	30.6%	86	69.4%	
Moderate Anemia	23	25.8%	66	74.2%	
Severe Anemia	2	12.5%	14	87.5%	
Gender					
Female					
Normal	33	36.3%	58	63.7%	5.985653, 0.112310
Mild anemia	17	42.5%	23	57.5%	
Moderate Anemia	16	26.7%	44	73.3%	
Severe Anemia	1	9.1%	10	90.9%	
Male					
Normal	103	44.6%	128	55.4%	13.354400, 0.003930
Mild anemia	21	25.0%	63	75.0%	
Moderate Anemia	7	24.1%	22	75.9%	
Severe Anemia	1	20.0%	4	80.0%	

of SARS-CoV-2, that is, death. Our results are supported by the results of Seung Mi Oh, *et al.*[7] who had also conducted a retrospective study on 733 admitted COVID-19 confirmed patients. Although their study showed anemia on admission as a predictor of higher mortality rate in hospitalized patients, the results were not significant for having severe outcomes during hospitalization. Similar results were observed in the study by Bellman *et al.*[8] who had also reported anemia as an independent predictor of mortality in 259 patients with COVID-19 (OR 3.729, CI [1.02–11.75], $P = 0.001$), but no association with functional iron deficiency.

COVID-19 directly infects cells expressing the angiotensin-converting enzyme 2 (ACE2). This activity has been observed in organs throughout the body,[9] leading to significant complications such as septic shock and multiple organ dysfunction[10,11] due to the reduced availability of ACE2 receptors which prevents vasodilation, further compounding peripheral tissue ischemia. Indeed, in the meta-analysis by Taneri *et al.*[12] that included 57,563 Covid-19 patients, the authors concluded that severity of the disease and the prognosis of the patients with COVID-19 might depend on lower hemoglobin levels as severe cases showed significantly lower hemoglobin levels than moderate cases. They explained the fact by stating that low hemoglobin levels, especially in high-risk populations could indicate that the patient could suffer from decreased capability of hemoglobin to support the increased oxygen demands of the peripheral tissues due to hyper metabolic state during infection.

In our study, the mean survival age of patients with anemia was significantly lower than that of patients without anemia. This calculation has been unique to our study as no other study with a similar objective has calculated the mean age of survival. This result may suggest that anemia has a higher risk of severity of COVID-19 than age alone.

The arterial oxygen content (CaO_2) consists mainly of oxygen (O_2) combined with hemoglobin (Hb). A minimum additional amount of O_2 is carried independent of Hb in physical solution. Therefore, the most effective way to increase CaO_2 is to increase Hb concentration. CaO_2 (mL O_2/dL) = (1.34 × hemoglobin g/dL × SaO_2%) + (0.0031 × $PaO_{2\,mmHg}$), where SaO_2 is the arterial oxygen saturation (%), PaO_2 is the arterial oxygen tension (mmHg) and 0.0031 is the solubility coefficient of oxygen in blood. 1.34 mL oxygen is carried by 1 gm of Hb and is called Hüfner's constant. Assuming a hemoglobin concentration of 15 g/dl and an oxygen saturation of 99%, the oxygen concentration of arterial blood is approximately 20 ml of O_2 per dL. CaO_2 depends primarily on the hemoglobin concentration. Therefore, people who are anemic may be suffering from inadequate oxygen delivery to tissues, regardless of adequate PaO_2 and SpO_2 values. Hemoglobin concentration is thus one of the most important markers of oxygen-carrying capacity in the blood. In infections like COVID-19, there occurs varying degrees of respiratory compromise and increased oxygen demand. Anemia, along with such infections, can further reduce oxygen delivery to peripheral tissues. Even transfusing packed red blood cells (PRBCs) will not help in Covid-19 crisis as PRBC is a stored product, where there is a gradual decrease in 2,3-diphosphoglycerate (2,3-DPG), which shifts the oxyhemoglobin curve to the left, thereby increasing the total oxygen carried, but not what is available for offloading into the tissues. CDC, till date, does not consider anemia as a risk factor for COVID-19. We believe that anemia and its severity may prove resourceful in managing hospitalized patients.

Hemoglobin estimation is a simple, quick, and easily available and reproducible test. With the bigger masses of infected people seeking hospitalization, hemoglobin estimation may be used as a method of triage. To the best of our knowledge, the results of our study are the first such conclusive data stating the independent role of anemia with deaths due to COVID-19 generated from India.

Our study has many limitations. First, the data was collected from the ICU of government hospitals of Jodhpur city alone. Hence, our results may have limited generalizability. However, as anemia is a global condition with higher prevalence in developing countries like India, our findings may have potential implications. Secondly, the study was performed during the peak of the pandemic, in which history-taking and notes were compromised to a certain extent. Thirdly, due to high patient and work loads, not all laboratory tests were carried out on all patients. Therefore, correlation of ferritin levels or other parameters of complete hemogram were not included in the analysis. Lastly, our main limitation was that we could not separate acute from chronic anemia or differentiate between the various types of anemia, which limits our interpretation. Nonetheless, our study suggests anemia on admission, regardless of its etiology, as a risk factor for severe outcomes in COVID-19 infection.

Conclusion

Anemia is a global disease associated with the prognosis of many clinical diseases, including diseases with respiratory compromises, such as COVID-19. We report that anemia on admission was independently associated with all-cause mortality in patients hospitalized with COVID-19. Estimation of hemoglobin on admission can be used as a tool for risk stratification in the upcoming waves of COVID-19.

Meanwhile, a general public advisory to improve their hemoglobin may be helpful in preventing severe COVID-19 infection in the future waves. Additional studies including more laboratory values and treatments received by patients should be the focus of future studies.

Acknowledgements

Dr Manish Goyal, for his expert help with statistical analysis in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. WHO Coronavirus (COVID-19) Dashboard. Covid19.who.int. 2021. Available from: https://covid19.who.int/. [Last accessed on 2021 Jun 28].
2. Benoit JL, Benoit SW, de Oliveira MHS, Lippi G, Henry BM. Anemia and COVID-19: A prospective perspective. J Med Virol 2021;93:708-11.
3. Gupta B, Jain G, Chandrakar S, Gupta N, Agarwal A. Arterial blood gas as a predictor of mortality in COVID pneumonia patients initiated on noninvasive mechanical ventilation: A retrospective analysis. Indian J Crit Care Med 2021;25:866-71.
4. Covid-19 and NCD risk factors. Who.int. 2021. Available from: https://www.who.int/docs/default-source/ncds/un-interagency-task-force-on-ncds/uniatf-policy-brief-ncds-and-covid-030920-poster.pdf?ua=1#:~:text=Obesity%20increases%20the%20risk%20for,the%20fight%20against%20COVID%2D19. [Last accessed on 2021 Jun 28].
5. COVID-19 and Your Health. Centers for Disease Control and Prevention. 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. [Last accessed on 2021 Jun 28].
6. Singh Y, Singh A, Rudravaram S, Soni KD, Aggarwal R, Patel N, *et al*. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as markers for predicting the severity in COVID-19 patients: A prospective observational study. Indian J Crit Care Med 2021;25:847-52.
7. Oh SM, Skendelas JP, Macdonald E, Bergamini M, Goel S, Choi J, *et al*. On-admission anemia predicts mortality in COVID-19 patients: A single center, retrospective cohort study. Am J Emerg Med 2021;48:140-7.
8. Bellmann-Weiler R, Lanser L, Barket R, Rangger L, Schapfl A, Schaber M, *et al*. Prevalence and predictive value of anemia and dysregulated iron homeostasis in patients with COVID-19 infection. J Clin Med 2020;9:2429.
9. Chu H, Chan JF-W, Yuen TT-T, Shuai H, Yuan S, Wang Y, *et al*. Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: An observational study. Lancet Microbe 2020;1:e14-23.
10. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-62.
11. Liu D, Wang Q, Zhang H, Cui L, Shen F, Chen Y, *et al*. Viral sepsis is a complication in patients with novel corona virus disease (COVID-19). Med Drug Discov 2020;8:100057.
12. Taneri PE, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz ZM, *et al*. Anemia and iron metabolism in COVID-19: A systematic review and meta-analysis. Eur J Epidemiol 2020;35:763-73.