ORIGINAL ARTICLE

Case fatality rate in patients of COVID-19 with anemia.

Samra Shahid[1], Afshan Noor[2], Amna Khalid[3], Ayesha Ellahi[4], Saleem Ahmed Khan[5], Afnan Naeem[6]

ABSTRACT... Objective: To analyze SARS-CoV2 patients who presented to Military Hospital Rawalpindi having normal hemoglobin levels and those with low hemoglobin. **Study Design:** Cross Sectional study. **Setting:** Pathology Laboratory, Military Hospital Rawalpindi, Pakistan. **Period:** March 2020 to July 2020. **Material & Methods:** Patients of both genders and all age groups with positive PCR for Corona virus were included. Patients of both the genders and all age groups with negative PCR for corona virus. 2ml blood sample was taken in EDTA tubes from the patients in wards and Intensive care unit and Hemoglobin level was checked using the Sysmex KX21 analyzer. **Results:** 400 COVID positive patients were studied with Hemoglobin ranging from 7.0g/dl to 17g/dl. It was seen that patients with low Hemoglobin levels were increasingly shifted to ventilators as compared to those with normal Hemoglobin whereas, the Ferritin level was raised in patients who expired. **Conclusion:** Most patients who expired due to COVID-19 virus infection had low hemoglobin level and high Ferritin level.

Key words: Anemia, COVID-19, Ferritin, SARS-COV-2.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) often results in Coronavirus disease 2019 (COVID-19), a disease that effect those with comorbidities like cardiovascular disease, diabetes mellitus and hypertension.[1,2] Different studies suggest increasing age as an important factor in the poor prognosis of the disease however, younger age group is not spared either.[2] In case of severe infection, COVID-19 can lead to multiple organ dysfunction syndrome, requiring ventilation or extracorporeal membrane oxygenation having low therapeutic efficacy.[3]

The pathophysiology of the disease is multifactorial and the reason behind the failure of the treatments remain unclear. Patients with severe COVID-19 infection present with an atypical form of the acute distress respiratory syndrome (ARDS)[4], where hypoxia develop due to reasons likely other than the alveolar problem.[5] Hypoxia plays a large role in the prognosis of the disease. Iron metabolism may be disturbed as in many inflammatory conditions.

Ferritin is an iron storing protein in the cytoplasm of the nucleated cells. An elevated level of Ferritin not only shows iron overload in the body but is also an acute phase reactant and indicates inflammation.[6] Various studies indicate that COVID-19 patients tend to have decreased hemoglobin levels representing the presence of anemia, and pathologically increased levels of ferritin.

Studies from Singapore, China and New York city suggest that patients who were shifted to Intensive care units had lower hemoglobin levels compared to non-Intensive care patients and so were the results in the patients who required hospitalization than those who were home managed.[7,8,9] Both anemia and hyperferritenemia, along with the individual's immunity, are strong predictors of mortality.[10,11] Anemia can result from iron-restricted erythropoiesis due to underlying alterations in iron metabolism. Increased ferritin levels may be indicative of a strong inflammatory reaction in COVID-19 or related to viral entry into the human body.[12,13]

1. FCPS, Assistant Professor Pathology, Army Medical College.
2. M.Phil, Lecturer, Federal Medical College Islamabad.
3. M.Phil, Assistant Professor Pathology, Abbotabad Medical College.
4. M.Phil, Lecturer, Army Medical College.
5. FCPS, Ph.D, Pro Vice Chancellor, National University of Medical Sciences.
6. M.Phil, Lecturer, Army Medical College.

Correspondence Address:
Dr. Samra Shahid
Department of Pathology
Armed Forces Institute of Pathology.
samrahshahid22@gmail.com

In the chronic illness the body via the mechanism of Hepcidin decreases the absorption of Iron into the body to arrest the growth of the pathogen.[12,13] Patients with COVID-19 infection already have hypoxia and Anemia may effect the oxygenation to organs further leading to a bad outcome.

In this article we analyzed SARS-CoV2 patients who presented to Military Hospital Rawalpindi having normal hemoglobin levels and those with low hemoglobin. Patients who were admitted to wards and Intensive Care units were assessed.

MATERIAL & METHODS

This Cross Sectional study was conducted at Pathology Laboratory, Military Hospital Rawalpindi, Pakistan from March 2020 to July 2020. Patients of both genders and all age groups with positive PCR for Corona virus were included in this study and patients of both the genders and all age groups with negative PCR for corona virus were excluded. 2ml blood sample was taken in EDTA tubes from the patients in wards and Intensive care unit and Hemoglobin level was checked using the Sysmex KX21 analyzer.

Data was collected and analysed using SPSS version 26. Mean + standard deviation of categorical variables was calculated by descriptive statistics. Comparison between the groups was calculated using chi-square test, one way ANOVA and independent-t test for the serum levels at two different points.

RESULTS

Total number of COVID-19 patients in our study was 500. Out of which male were 441 (88.2%) and female were 59 (11.8%) having male predominance of 7.5:1. The mean of age was 50.7 + 16 years and ranged between 11 to 90 years. The age was further grouped in the different subgroups having < 29 years was 50 (10%), having 30-39 years was 96 (19.2%), 40-49 years was 96 (19.2%), 50-59 years 97 (19.4%), 60-69 years 92 (18.4%) and > 70 years was 69 (13.8%). Highest number of mortality was observed in the group having age ranged from 60-69 years with a total number of 53 (30.8%), followed by group having 50-59 years of 41 (23.8%) and those

having age above > 70 was 39 (22.7%). Table-I

The age was shown to have significant finding in the outcome group of survival and non-survival having p-value <0.0001 similarly gender also had significant results within the outcome group of survivor and non-survivors as per Table-II (p-value = <0.0001).

Patients (n= 500)	
Age, years (Mean± SD)	50.7 + 16
Range of age (years old)	11- 90
< 29	50 (10%)
30-39	96 (19.2%)
40-49	96 (19.2%)
50-59	97 (19.4)
60-69	92 (18.4%)
> 70	69 (13.8%)
Sex %	
Male	441 (88.2%)
Female	59 (11.8%)
Comorbidities %	
Yes	237 (47.4%)
No	263 (52.6%)
Outcome %	
Survivors	172 (34.4%)
Non-survivors	328 (65.6%)
Blood Parameters (Mean± SD)	
Hemoglobin g/dl	13.3 + 2.33
Red blood cells x 10^6 /ml	4.37 + 1.28
Serum Ferritin mg/dl	650.6 + 1370.2
Patients (n= 500)	

Table-I. Demographics, baseline characteristics and outcomes of 500 laboratory-confirmed patients admitted to the hospital.

Outcome of our patients were grouped into two groups, those who survived were 328 (65.6%) and the non-survivors were 172 (34.4%). Patients having underlying comorbidities were 172 (34.4%) and those without any comorbidity were 328 (65.6%). Significant findings were also observed in the outcome group of survivors and non-survivors when compared with age, hemoglobin, RBC count and serum ferritin levels as given in Table-III (p-value = <0.0001).

The cause of death in expired patients of 172 (34.4%) was acute respiratory distress syndrome (ARDS), multiple organ damage (MOD), disseminated intravascular coagulation (DIC) and pulmonary embolism (PE). Total number of ARDS death cases was found to be highest, i.e., 74 (14.8%), MOD was 47 (9.4%) DIC was 32 (6.4%) and PE was a total of 19 (3.8%) (P-value <0.0001). Out of 172 total expired patients a highest number of deaths were seen among those who already had underlying comorbidities as compared to those having no comorbidities i.e; 149 (62.8% vs 23 (37.2%).

Age range group and comorbidities compared with the cause of death had very significant findings as per Table-IV (p-value < 0.0001). Age of the expired patients all had age above 50 years onwards while least number was observed age below 50 years.

Blood parameters results of hemoglobin (Hb) having mean of 13.3 ± 2.33, red blood cell count (RBC) was 4.37 ± 1.28 and serum ferritin levels was 650.6 ± 1370.2. These blood parameters compared in the group of survivors and non-survivors has shown to have very significant results as given table-II having p-value of <0.0001. Serum ferritin was markedly increased in the severe patients as well as non-survivors and all having significant results having p-value < 0.0001. Serum ferritin levels all had very significant results associated with compared with the comorbidities, outcome group of survivors and non-survivors, red blood cell count levels, hemoglobin levels while it did not have significant results with gender and age as given in Table-V (p-value 0.95 and 0.28 respectively).

The mean ferritin in non survivors was 1435.60 while the mean ferritin in survivors was far less that is 238.9mg/l making it a significant result with the p value being less than 0.001.

237(47.4%) patients had comorbidities out of the total 500 while 263(52.6%) had no comorbid conditions. Discussing the non survivors 145(84.3%) were males while 27(15.7%) were females 149(86.6%) had comorbidities while 23(13.4%) had no comorbidities.

	Total	Survivors	Non-survivors	P-Value
Age years (M+SD)	50.7 + 16	46.20 + 15.36	59.07 + 13.49	<0.0001
Range of age (years old)		11- 90		
< 29	50 (10%)	46 (14%)	4 (2.3%)	
30-39	96 (19.2%)	85 (25.9%)	11 (6.4%)	
40-49	96 (19.2%)	72 (22%)	24 (14%)	<0.0001
50-59	97 (19.4%)	56 (17.1%)	41 (23.8%)	
60-69	92 (18.4%)	39 (11.9%)	53 (30.8%)	
>70	69 (13.8%)	30 (9.1%)	39 (22.7%)	
Gender (n, %) Male Female	441 (88.2%) 59 (11.8%)	296 (90.2%) 32 (9.8%)	145 (84.3%) 27 (15.7%)	0.037
Comorbidities (n, %) Yes No	172 (34.4%) 328 (65.6%)	88 (26.8%) 240 (73.2%)	149 (86.6%) 23 (13.4%)	< 0.0001
Blood parameters (M +SD) Hemoglobin g/dl	13.3 + 2.33	14.174 + 1.62	11.623 + 2.56	<0.0001
Red blood cell count x10^6/ml	4.37 + 1.28	4.876 + 0.98	3.41 + 1.25	<0.0001
Serum Ferritin mg/dl	650.6 + 1370.2	238.97+ 241.05	1435.06 + 2103.44	<0.0001

Table-II. Association between baseline variables and outcome of the COVID-19 disease.

Parameters	Sig (2-tailed)	Mean diff	Std Error Diff	95% Confidence Interval	
				Upper	Lower
Age	<0.0001	12.872	1.389	10.14	15.60
Hb	<0.0001	-2.550	0.188	-2.92	-2.17
RBC count	<0.0001	-1.46	0.102	-1.66	-1.25
Serum Ferritin	<0.0001	1196.09	117.48	965.26	1426.91

Table-III. Independent t sample test for the given parameters.

Age Range	Comorbidities		Total	P-Value
	Yes	No		
< 29	4 (1.7%)	46 (17.5%)	50 (10%)	
30-39	9 (3.8%)	87 (33.1%)	96 (19.2%)	
40-49	30 (12.7%)	66 (25.1%)	96 (19.2%)	
50-59	49 (20.7%)	48 (18.3%)	97 (19.4%)	<0.0001
60-69	77 (32.5%)	15 (5.7%)	92 (18.4%)	
>70	68 (28.7%)	01 (0.4%)	69 (13.8%)	

Table-IV. Comparison of different age groups in COVID-19 patients along with existing comorbidities.

Parameters		Sum of squares	df	Mean square	F	Sig
Gender	between groups	32.93	341	0.97	0.799	0.95
	within groups	19.10	158	0.12		
	total	52.03	499			
Outcome	between groups	98.19	341	0.28	3.109	<0.0001
	within groups	14.63	158	0.09		
	total	112.8	499			
Comorbidities	between groups	93.91	341	0.27	1.41	0.007
	within groups	30.75	158	0.19		
	total	124.66	499			
Age	between groups	89049.30	341	261.14	1.08	0.28
	within groups	38001.75	158	240.51		
	total	127051.06	499			
Hemoglobin	between groups	2074.61	341	6.08	1.47	<0.0001
	within groups	653.83	158	4.13		
	total	2728.44	499			
Red blood cell count	between groups	650.01	341	1.90	1.69	<0.0001
	within groups	177.48	158	1.12		
	total	827.49	499			

Table-V. Comparison of serum ferritin with other variables by using one-way ANOVA.

The mean ferritin in non survivors was 1435.60 while the mean ferritin in survivors was far less that is 238.9mg/l making it a significant result with the p value being less than 0.001.

237(47.4%) patients had comorbidities out of the total 500 while 263(52.6%) had no comorbid conditions. Discussing the non survivors 145(84.3%) were males while 27(15.7%) were females 149(86.6%) had comorbidities while 23(13.4%) had no comorbidities.

DISCUSSION

In this study it was found that the severe cases or expired patients had low haemoglobin and high levels of serum ferritin in both genders. Raised level of ferritin was due to inflammatory response mediated by COVID and other co morbidities and it increased with age in both males and females.[14] Decrease in Haemoglobin can result in low oxygen carrying capacity, which cannot support the increased peripheral demand in hyper metabolic state. Therefore, it results in septic shock, viral sepsis or multiple organ failure in patients with

comorbidities such as, cardio vascular disease, hypertension, chronic obstructive pulmonary disease (COPD), chronic liver disease or chronic renal disease.[15] The prognosis depends on meeting the oxygen demands in patients with pneumonia or acute respiratory distress syndrome to avoid hypoxia and ischemia.[15,16] The outcome was poor in patients with anaemia and high serum ferritin levels predicted mechanical ventilation.[17]

Comparing our results with other studies Masood Faghih Dinevari et al in his article narrated that the frequency of fatal cases, admissions in ICU and ventilator support were higher in anaemic patients than in non-anaemic patients (p< 0.001).[18]

Another article published by Abdul Rahman A. Algassim et al also narrated that Anaemic COVID-19 patients admitted in the Intensive care unit had a higher mortality compared with non-anaemic ICU patients (p=0.0104)19. However, it could not consistently predict death in all patients. Diagnostic criteria could not be established in such patients but high levels of serum ferritin were associated in forecasting fatality but not all cases of raised serum ferritin expired.[17,18] There is marked raised levels of inflammatory cytokines and biomarkers in hyper inflammatory phase, such as interleukin (IL) 2, IL 6, IL 7, macrophage inflammatory protein, granulocytes colony stimulating factor, TNF- α, CRP, D dimer and ferritin. This results in cardiovascular collapse, pulmonary failure and multi organ failure.[20,21]

However, high levels of serum ferritin were autonomously correlated to acute respiratory distress syndrome (ARDS) in COVID patients, according to our study.

CONCLUSION
Most patients who expired due to Covid 19 virus infection had low hemoglobin level and high Ferritin level.

REFERENCES

1. Wang L, Duan Y, Zhang W, Liang J, Xu J, Zhang Y, et al. **Epidemiologic and clinical characteristics of 26 cases of Covid-19 arising from patient-to-patient transmission in Liaocheng.** China Clin Epidemiol. 2020; 12:387–91.

2. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. **Prevalence of comorbities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis.** Int J Infect Dis. 2020; 94:91–5.

3. 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(10229):1054–62.

4. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. **Covid-19 does not lead to a "Typical" Acute Respiratory Distress Syndrome.** Am J Respir Crit Care Med. 2020; 201(10):1299–1300.

5. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, et al. **Hypoxaemia related to COVID-19: Vascular and perfusion abnormalities on dual-energy CT.** Lancet Infect Dis. 2020 (in press).

6. Kell DB, PretoriusE. **Serum ferritin is an important inflammatory disease marker, as it is mainly a lekeage product from damaged cells.** Metallomics 2014; 6(1): 748-73.

7. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. **Hematologic parameters in patients with COVID-19 infection.** Am J Hematol. 2020; 95(6):E131–4.

8. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. **Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up.** J Infect. 2020; 80(6):639–45.

9. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J. **Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area.** Jama. 2020 May 26; 323(20):2052-9.

10. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. **Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study.** BMJ. 2020; 368:m1091.

11. Bennett TD, Hayward KN, Farris RW, Ringold S, Wallace CA, Brogan TV. **Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients.** PediatrCrit Care Med. 2011; 12(6):e233–e236236.

12. Liu Z, Sun R, Li J, Cheng W, Li L. **Relations of anemia with the all-cause mortality and cardiovascular mortality in general population: A meta-analysis.** Am J Med Sci. 2019; 358(3):191–9.

13. Kernan KF, Carcillo JA. **Hyperferritinemia and inflammation.** Int Immunol. 2017; 29(9):401–9.

14. Wessling-Resnick M. **Crossing the Iron Gate: Why and how transferrin receptors mediate viral entry.** Annu Rev Nutr. 2018; 38:431–58.

15. Taneri PE, Gomez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Wyssmann BM, Kopp-Heim D, Hautz WE, Eisenga MF, Franco OH, Glisic M. **Anemia and iron metabolism in COVID-19: A systematic review and meta-analysis.** medRxiv. 2020 Jan 1.

16. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L. **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study.** The lancet. 2020 Mar 11.

17. Liu D, Wang Q, Zhang H, Cui L, Shen F, Chen Y, Sun J, Gan L, Sun J, Wang J, Zhang J. **Viral sepsis is a complication in patients with Novel Corona Virus Disease (COVID-19).** Medicine in Drug Discovery. 2020 Dec 1; 8:100057.

18. Faghih Dinevari M, Somi MH, Sadeghi Majd E, Abbasalizad Farhangi M, Nikniaz Z. **Anemia predicts poor outcomes of COVID-19 in hospitalized patients: A prospective study in Iran.** BMC infectious diseases. 2021 Dec; 21(1):1-7.

19. Algassim AA, Elghazaly AA, Alnahdi AS, Mohammed-Rahim OM, Alanazi AG, Aldhuwayhi NA, Alanazi MM, Almutairi MF, Aldeailej IM, Kamli NA, Aljurf MD. **Prognostic significance of hemoglobin level and autoimmune hemolytic anemia in SARS-CoV-2 infection.** Annals of hematology. 2021 Jan; 100(1):37-43.

20. Feld J, Tremblay D, Thibaud S, Kessler A, Naymagon L. **Ferritin levels in patients with COVID-19: A poor predictor of mortality and hemophagocytic lymphohistiocytosis.** International journal of laboratory hematology. 2020 Dec; 42(6):773-9.

21. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. **Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State.** Jama. 2020 Apr 28; 323(16):1612-4.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Samra Shahid		
2	Afshan Noor		
3	Amna Khalid	All authors have contributed equally.	
4	Ayesha Ellahi		
5	Saleem Ahmed Khan		
6	Afnan Naeem		