Journal of Thrombosis and Thrombolysis (2022) 53:113–117
https://doi.org/10.1007/s11239-021-02516-1

U shape association of hemoglobin level with in-hospital mortality for COVID-19 patients

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Accepted: 21 June 2021 / Published online: 2 July 2021

Abstract
Our hypothesis was that high hemoglobin (Hb) level might be associated with hypercoagulable state and death due to COVID-19. Of the 9467 hospitalized COVID-19 patients, patients were subdivided into 5 groups based on the level of Hb; Hb < 10 g/dL, 10 g/dL ≤ Hb < 12 g/dL, 12 g/dL ≤ Hb < 14 g/dL, 14 g/dL ≤ Hb < 16 g/dL, and Hb ≥ 16 g/dL. Compared to patients with 12 g/dL ≤ Hb < 14 g/dL, patients with Hb ≥ 16 g/dL had significantly higher adjusted in-hospital mortality (OR [95% CI] 1.62 [1.15–2.27], P = 0.005).

Keywords COVID-19 · Hemoglobin · Mortality

Abbreviations

CI	Confidential interval
COVID-19	Coronavirus disease 2019
Hb	Hemoglobin
OR	Odds ratio

Highlights

- We analyzed 9467 patients dividing subgroups based on hemoglobin.
- Patients with hemoglobin ≥ 16 g/dL had higher risk adjusted in-hospital mortality.
- Treatment strategies based on hemoglobin would be warranted.

Introduction

Anemia is considered to be an independent predictor of mortality due to coronavirus disease 2019 (COVID-19) [1]. However, it remains uncertain if the association between hemoglobin (Hb) level and mortality is linear or non-linear. We hypothesized that high Hb level might be associated with hypercoagulable state and death since COVID-19 increases coagulopathy resulting in systemic thrombosis [2]. We aimed to investigate whether high Hb level was associated with in-hospital mortality among patients hospitalized with COVID-19.

Methods

This retrospective study was conducted by review of the medical records of 9542 hospitalized patients who were discharged between March 1st, 2020 and March 30th 2021, with laboratory confirmed COVID-19 in the Mount Sinai Health System [3]. After excluding patients with Hb < 6 g/dL or > 19 g/dL as outliners, the final cohort of our study included 9467 patients. Patients were subdivided into five groups based on Hb level: Hb < 10 g/dL, 10 g/dL ≤ Hb < 12 g/dL, 12 g/dL ≤ Hb < 14 g/dL, 14 g/dL ≤ Hb < 16 g/dL, and 16 g/dL ≤ Hb [4]. The primary outcome of interest was in-hospital mortality. Secondary outcomes were acute kidney injury and acute venous thromboembolism. Acute kidney injury was defined as a 50% or 0.3 mg/dL increase of creatinine level [5].

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A logistic regression model was created to estimate the association between in-hospital mortality and Hb level where the reference level was 12 g/dL ≤ Hb < 14 g/dL. In addition to Hb subgroups, the following variables were used for a logistic regression model: age, sex, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, obesity, hypertension, diabetes mellitus, human immunodeficiency virus, cancer, atrial fibrillation, coronary artery disease, heart failure, peripheral vascular disease, chronic viral hepatitis, alcoholic/non-alcoholic liver disease, estimated glomerular filtration rate, blood urea nitrogen, white blood cell count, platelet, C reactive protein, d-dimer, vital signs (temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, oxygen saturation) at admission, endotracheal intubation, intensive care unit admission, treatment with therapeutic anticoagulation, prophylactic anticoagulation, steroid, interleukin-6 inhibitor, remdesivir, and convalescent plasma. The Modification of Diet in Renal Disease equation was used to estimate glomerular filtration rate [6].

Additionally, we checked the association between Hb level and risk-adjusted in-hospital mortality, where Hb was analyzed as a continuous variables using a smooth spline curve. All statistical analyses were performed using R (version 3.6.2, R). P values < 0.05 considered statistically significant.

This study was approved by the institutional review boards of Icahn School of Medicine at Mount Sinai (#2,000,495) and conducted in accordance with the principles of the Declaration of Helsinki. The waiver of patients' informed consent was also approved by the institutional review boards.

Results

Table 1 shows baseline characteristics stratified by Hb level. Patients with high Hb were younger, more likely to be male, and had fewer comorbidities. Patients with high Hb had relatively lower C reactive protein and d-dimer levels (Table 1). The treatments and in-hospital outcomes by Hb levels were also shown in Table 1. Patients with the lowest and highest Hb had higher in-hospital mortality. The incidences of acute kidney injury were higher in patients with lower Hb. The proportions of acute venous thromboembolism were not different across the Hb groups.

Notably, compared to patients with Hb between 12 and 14 g/dL, patients with Hb ≥ 16 g/dL had significantly higher risk-adjusted in-hospital mortality (odds ratio (OR) [95% confidential interval (CI)] 1.62 [1.15–2.27], P = 0.005) as well as those with Hb < 10 g/dL (OR [95% CI] 1.61 [1.24–2.08], P < 0.001) and those with 10 g/dL ≤ Hb < 12 g/dL (OR [95%CI] 1.30 [1.05–1.60], P = 0.014), but not those with 14 g/dL ≤ Hb < 16 g/dL (OR [95%CI] 1.08 [0.88–1.32], P = 0.48). The smooth spline curve showed the U curve association of Hb level with risk-adjusted in-hospital mortality (Fig. 1). The details of logistic regression models are shown in Supplemental Table 1.

Discussion

Although anemia is already considered to be an independent predictor of mortality due to COVID-19 [1], showing that high hemoblobin is also associated with in-hospital mortality of COVID-19 in our study is valuable. High Hb levels themselves might cause systemic thrombosis. The previous case reports showed that polycythemia vera could be a reason for the thrombosis due to COVID-19 [7, 8]. Although we could not reveal that the incidences of acute venous thromboembolism were different between the Hb subgroups, we assume there might be more microthrombi in lungs among patients with high hemoglobin, which could contribute to hypoxia and death [9].

Our study has limitations. This is a retrospective observational study. Despite rigorous adjustments, unmeasured confounders could not be adjusted. In addition, we did not have the information on the presence of myeloproliferative disease, erythropoietin supplementation, and the causes of death.

Table 1 Baseline characteristics and in-hospital outcomes of patients hospitalized due to COVID-19 infection and stratified by hemoglobin level

	Hb < 10 g/dL N = 1045	Hb 10- 12 g/dL N = 1871	Hb 12- 14 g/dL N = 3408	Hb 14- 16 g/dL N = 2555	Hb ≥ 16 g/dL N = 588	P value
Demographics and comorbidities						
Age (years), mean (SD)	66.9 (16.5)	67.7 (17.2)	65.4 (16.7)	62.5 (16.8)	60.6 (17.2)	< 0.001
Male, n (%)	492 (47.1)	760 (40.6)	1600 (46.9)	1834 (71.8)	498 (84.7)	< 0.001
Race, n (%)						< 0.001
White	257 (24.6)	534 (28.5)	980 (28.8)	667 (26.1)	148 (25.2)	
African American	345 (33.0)	510 (27.3)	814 (23.9)	504 (19.7)	107 (18.2)	
Hispanic	240 (23.0)	442 (23.6)	833 (24.4)	735 (28.8)	169 (28.7)	
Asian	56 (5.4)	112 (6.0)	203 (6.0)	153 (6.0)	33 (5.6)	
Others	147 (14.1)	273 (14.6)	578 (17.0)	496 (19.4)	131 (22.3)	
Comorbidities						
COPD, n (%)	58 (5.6)	109 (5.8)	128 (3.8)	108 (4.2)	18 (3.1)	0.001
Hypertension, n (%)	525 (50.2)	837 (44.7)	1155 (33.9)	761 (29.8)	161 (27.4)	< 0.001
Diabetes mellitus, n (%)	366 (35.0)	579 (30.9)	706 (20.7)	452 (17.7)	124 (21.1)	< 0.001
Obstructive sleep apnea, n (%)	31 (3.0)	64 (3.4)	67 (2.0)	54 (2.1)	7 (1.2)	0.002
Obesity, n (%)	99 (9.5)	182 (9.7)	300 (8.8)	216 (8.5)	37 (6.3)	0.11
Atrial fibrillation, n (%)	131 (12.5)	183 (9.8)	229 (6.7)	172 (6.7)	46 (7.8)	< 0.001
Heart failure, n (%)	198 (18.9)	259 (13.8)	240 (7.0)	115 (4.5)	32 (5.4)	< 0.001
Coronary artery disease, n (%)	233 (22.3)	347 (18.5)	434 (12.7)	296 (11.6)	66 (11.2)	< 0.001
Vital signs						
Respiratory rate (/min), mean (SD)	20.4 (4.8)	20.5 (5.0)	20.6 (5.1)	21.0 (6.1)	21.2 (6.3)	0.001
O_2 Saturation (%), mean (SD)	82.7 (19.5)	84.0 (18.1)	84.8 (16.1)	83.6 (17.7)	83.1 (19.0)	0.003
Blood tests						
White blood cell (K/μL), median [IQR]	7.6 [5.1, 11.2]	7.4 [5.3, 10.5]	7.1 [5.3, 10.0]	7.5 [5.6, 10.4]	7.9 [5.9, 11.3]	< 0.001
Hemoglobin (g/dL), median [IQR]	8.9 [8.1, 9.5]	11.1 [10.6, 11.6]	13.0 [12.5, 13.5]	14.7 [14.3, 15.2]	16.5 [16.2, 17.0]	< 0.001
Platelet (K/μL), median [IQR]	218.0 [149.0, 305.0]	211.0 [157.0, 281.0]	205.0 [157.0, 265.0]	201.0 [155.0, 256.0]	183.0 [143.0, 247.0]	< 0.001
eGFR (ml/min./1.73m^2), median [IQR]	37.7 [15.4, 75.1]	55.0 [29.2, 86.5]	73.2 [49.8, 97.3]	76.0 [54.2, 96.5]	73.9 [52.8, 90.7]	< 0.001
C reactive protein (mg/L), median [IQR]	97.2 [37.0, 183.9]	82.0 [34.9, 164.1]	85.7 [36.4, 162.2]	92.8 [43.1, 171.7]	83.4 [38.5, 149.6]	0.001
D-Dimer (μg/mL), median [IQR]	2.19 [1.18, 3.81]	1.76 [0.98, 3.09]	1.24 [0.70, 2.30]	1.11 [0.65, 2.06]	1.16 [0.66, 2.47]	< 0.001
Treatment						
Therapeutic anticoagulation, n (%)	411 (39.3)	705 (37.7)	1152 (33.8)	893 (35.0)	213 (36.2)	0.004
Prophylactic anticoagulation, n (%)	465 (44.5)	981 (52.4)	1970 (57.8)	1465 (57.3)	311 (52.9)	< 0.001

Table 1 (continued)

	Hb < 10 g/dL N = 1045	Hb 10- 12 g/dL N = 1871	Hb 12- 14 g/dL N = 3408	Hb 14- 16 g/dL N = 2555	Hb ≥ 16 g/dL N = 588	P value
Steroid treatment, n (%)	426 (40.8)	900 (48.1)	1740 (51.1)	1360 (53.2)	299 (50.9)	< 0.001
IL-6 inhibitor, n (%)	16 (1.5)	39 (2.1)	134 (3.9)	115 (4.5)	19 (3.2)	< 0.001
Convalescent Plasma, n (%)	103 (9.9)	212 (11.3)	416 (12.2)	310 (12.1)	69 (11.7)	0.29
Use of Remdesivir, n (%)	85 (8.1)	246 (13.1)	640 (18.8)	514 (20.1)	107 (18.2)	< 0.001
In-hospital outcomes						
In-hospital mortality	348 (33.3)	494 (26.4)	681 (20.0)	530 (20.7)	148 (25.2)	< 0.001
Intensive care unit admission	234 (22.4)	363 (19.4)	632 (18.5)	530 (20.7)	140 (23.8)	0.005
Endotracheal intubation	176 (16.8)	242 (12.9)	413 (12.1)	336 (13.2)	87 (14.8)	0.002
Acute kidney injury	498 (47.9)	636 (34.8)	770 (23.0)	556 (21.9)	141 (24.1)	< 0.001
Acute venous thromboembolism	14 (1.3)	24 (1.3)	42 (1.2)	23 (0.9)	10 (1.7)	0.48

COPD chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin, *IL* interleukin, *IQR* interquartile range, *SD* standard deviation

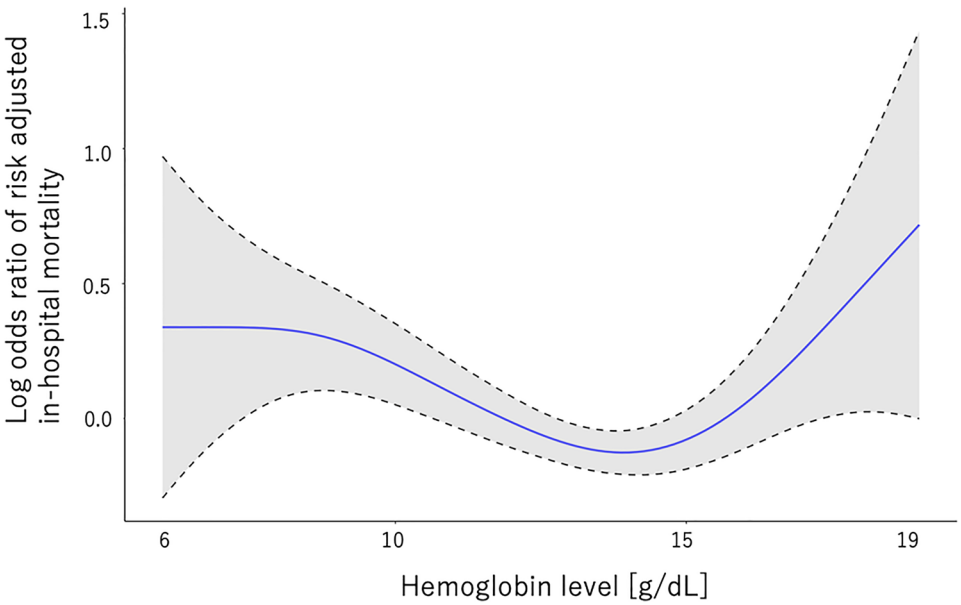

Fig. 1 The association of hemoglobin level and risk adjusted in-hospital mortality (*y* axis: log odds ratio of adjusted in-hospital mortality, *x* axis: hemoglobin level [g/dL])

Conclusion

High mortality is observed in patients with high Hb levels as well as those with low Hb levels.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11239-021-02516-1.

Authors contribution TK, MT, NE, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: TK. Data Curation: TK, MT, NE. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: TK. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: TK, MT. Administrative, technical, or material support: NE. Study supervision: NE.

Funding None.

Declarations

Ethical approval This study was approved by the institutional review boards of Icahn School of Medicine at Mount Sinai (#2000495) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed consent The waiver of patients' informed consent was also approved by the institutional review boards.

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