The association of hemoglobin drop with in-hospital outcomes in COVID-19 patients

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Abstract

Background: Bleeding events can be critical in hospitalized patients with COVID-19, especially those with aggressive anticoagulation therapy.

Aim: We aimed to investigate whether hemoglobin drop was associated with increased risk of acute kidney injury (AKI) and in-hospital mortality among patients with COVID-19.

Design: Retrospective cohort study

Methods: This retrospective study was conducted by review of the medical records of 6,683 patients with laboratory confirmed COVID-19 hospitalized in the Mount Sinai Health system between March 1st, 2020 and March 30th 2021. We compared patients with and without hemoglobin drop >3g/dL during hospitalization within a week after admissions, using inverse probability treatment weighted analysis (IPTW). Outcomes of interest were in-hospital mortality and AKI which was defined as serum creatine change of 0.3 mg/dL increase or 1.5 times baseline.

Results: Of the 6,683 patients admitted due to COVID-19, 750 (11.2%) patients presented with a marked hemoglobin drop. Patients with hemoglobin drop were more likely to receive therapeutic anticoagulation within two days after admissions. Patients with hemoglobin drop had higher crude in-hospital mortality (40.8% versus 20.0%, P<0.001) as well as AKI (51.4% versus 23.9%, P<0.001) compared to those without. IPTW analysis showed that hemoglobin drop was associated with higher in-hospital mortality compared to those without (odds ratio (OR) [95% confidential interval (CI)]: 2.21 [1.54-2.88], P<0.001) as well as AKI (OR [95% CI]: 2.79 [2.08-3.73], P<0.001).

Conclusions: Hemoglobin drop during COVID-19 related hospitalizations was associated with a higher risk of AKI and in-hospital mortality.

Introduction

Inflammation and cytokine storm are considered to be associated with increased mortality due to Coronavirus disease 2019 (COVID-19). Currently steroids are the main treatment for critically ill patients with COVID-19 (1). Coagulopathy is also associated with increased risk of death due to COVID-19 (1, 2), and therefore, therapeutic or prophylactic anticoagulation might be beneficial for the treatment of COVID-19 (2). However, bleeding events are of concern in COVID-19 patients with impaired coagulation ability, especially those with aggressive anticoagulation therapy (3, 4).

Anemia in critical illness is a common condition and its cause is often multifactorial affecting mortality (5). The causes of anemia are often multifactorial. In addition, in the field of cardiovascular diseases, hemoglobin drop is known to be associated with worse long-term outcome during treatment of acute coronary syndrome (6) and higher incidence of acute kidney injury (AKI) during a periprocedural period in percutaneous coronary intervention. Hemoglobin drop due to periprocedural blood loss is leading to intravascular volume loss that is an additional insult to kidneys when kidneys are exposed to iodine contrast (6-8). Hemoglobin drop in the setting of critical illness when various potentially nephrotoxic medications are given may have a mechanism similar to periprocedural hemoglobin drop in percutaneous coronary intervention. Additionally, AKI itself is known to be associated with higher mortality in COVID-19 patients (9).

However, the effect of hemoglobin drop in the context of COVID-19 infection has not been investigated.

Therefore, we aimed to investigate whether hemoglobin drop was associated with AKI and in-hospital mortality among patients with COVID-19. Our hypothesis was that hemoglobin drop might be associated with worse in-hospital outcomes of COVID-19.

Methods:

Data source and study population

This retrospective study was conducted by review of the medical records of 9,965 hospitalized patients who were discharged between March 1st 2020 and March 30th 2021, with laboratory confirmed COVID-19 in the Mount Sinai Health system (10-17). Identification of COVID-19 was based on a nasopharyngeal swab, which was tested using a polymerase chain reaction. Patients less than 18 years of age were excluded (N=51). Patients who were transferred to other facilities were also excluded (N=349). In addition, patients who had less than two hemoglobin measurements within a week after hospitalizations were also excluded (N=881) since we aimed to investigate the effect of hemoglobin drop during the early phase of hospitalization. In addition, we also excluded 1,040 patients who were discharged (dead or alive) within two days because we could not estimate the effect of hemoglobin drop during the early phase of hospitalization. Moreover, we excluded patients with hemoglobin level <10 g/dL (N=889) to estimate the effect of hemoglobin drop >3 g/dL. Hemoglobin cut off 7 g/dL is usually used for the cut off for transfusion which mitigate the trend of hemoglobin (18). Moreover, we excluded the patients with hemoglobin drop >6 g/dL since it is more than three times the standard deviation (N=72). Thus, the final cohort of our study consisted of 6,683 patients.

Patients' electronic medical records were reviewed and demographics, comorbidities, vital signs, laboratory data, and clinical outcomes were extracted.

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Exposure definition

In the main analysis, patients were stratified into the two groups, those with hemoglobin drop and those without it. The "hemoglobin drop" was defined as decrease in serum hemoglobin level by ≥3 g/dL from the baseline level at admission within a week which could be used for the estimate of in-hospital mortality. The cut off 3 g/dL was defined according to the definition used in a previous study in the field of cardiovascular disease (6). We also examined an association between the extent of hemoglobin change and the study outcomes, creating a smooth spline curve, as explained later in the statistical analysis section.

Outcomes

The primary outcome of interest was in-hospital mortality. Secondary outcomes were AKI and liver injury. AKI was defined according to KDIGO criteria stratified by creatinine level; stage 1: 1.5-1.9 times baseline or ≥0.3mg/dL increase; stage 2: 2.0-2.9 times baseline; stage 3: 3 times or creatinine >4.0mg/dL (19, 20). Liver injury was defined as alanine aminotransferase with more than 5 times of upper normal limits.

Covariates

Comorbidities were characterized based on the International Classification of Disease (ICD) 10 codes. All vital signs and blood tests were recorded at time of admission. Further, we controlled for relevant treatments, including systemic steroids, therapeutic anticoagulation, prophylactic anticoagulation, convalescent plasma, and interleukin-6 inhibitor (Tocilizumab). Therapeutic anticoagulation was defined as apixaban, dabigatran, rivaroxaban (excluding 2.5 mg as prevention of atherosclerotic cardiovascular events) (21), edoxaban, warfarin, and enoxaparin (as therapeutic dose), intravenous continuous unfractionated heparin, and argatroban. Prophylactic anticoagulation was defined as subcutaneous heparin in prophylactic dose. Steroids were defined as treatment with systemic betamethasone, dexamethasone, hydrocortisone, prednisone, prednisolone, and methylprednisolone. We collected the data of therapeutic and prophylactic anticoagulation which were given within two days since admissions because we aimed to investigate its effect for hemoglobin drop within a week.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median [interquartile range] depending on the data distribution, and categorical variables were expressed as percentages. Differences in baseline characteristics between groups were evaluated, using the χ^2 test for categorical variables.

We performed inverse probability weighted analysis. The following variables were used to estimate propensity score: age, sex, race, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, obesity, hypertension, diabetes mellitus, human

immunodeficiency virus, cancer, atrial fibrillation, coronary artery disease, heart failure, peripheral artery disease, chronic viral hepatitis, alcoholic/non-alcoholic liver disease, estimated glomerular filtration rate (eGFR), blood urea nitrogen, white blood cell count, hemoglobin and platelet, vital signs, 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 eGFR (20).

In addition, we also created a smooth spline describing the association between the extent of the hemoglobin change and adjusted odds ratio of hospital mortality. Adjusted odds ratio was calculated with a multivariate logistic regression model using the variables same as the variables to estimate propensity score.

As an additional sensitivity analysis, missing data was imputed using mice package and IPTW analysis was performed (R software). All statistical analyses were performed using R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria). P-values <0.05 considered statistically significant.

Results

Of the 6,683 patients admitted due to COVID-19, 750 (11.2%) had hemoglobin drop by 3 g/dL. Baseline characteristics and vital signs across study groups are reported in Table 1. Length of hospital stay and number of hemoglobin measurements during hospitalization were also significantly different (Table 1). Vital signs at admission were significantly different between patients with and without hemoglobin drop: the respiratory rate at admission was 20.0 [18.0, 24.0] versus 20.0 [18.0, 22.0] /min. and oxygen saturation

level was 85.0 [72.0, 91.0] versus 90.0 [84.0, 92.0] % for patient with hemoglobin drop versus those without, respectively (both P<0.001). Patients with hemoglobin drop had higher white blood cell count, hemoglobin, blood urea nitrogen, d-dimer, C reactive protein, and lower eGFR compared to those without hemoglobin drop (Table 1). Patients with hemoglobin drop were more likely to receive therapeutic anticoagulation treatment within two days after admissions (Table 1).

Patients with hemoglobin drop had higher observed in-hospital mortality compared to those without hemoglobin drop (40.8% versus 20.0%, P<0.001) as well as AKI (51.4% versus 23.9%, P<0.001) (Table 2). Interestingly, patients with hemoglobin drop and AKI had higher in-hospital mortality compared to those with hemoglobin drop but without AKI (60.6% versus 20.4%, P<0.001).

Using IPTW analysis, we achieved a good balance between study groups: the standardized mean difference was <0.10 for the majority of covariates (Table 1). Notably, hemoglobin drop was associated with higher in-hospital mortality compared to those without (odds ratio (OR) [95% confidential interval (CI)]: 2.21 [1.54-2.88], P<0.001) as well as higher incidence of AKI (OR [95% CI]: 2.79 [2.08-3.73], P<0.001) after IPTW adjustments. Multiple imputation also showed similar results for in-hospital mortality (OR [95% CI]: 1.79 [1.38−2.33], P<0.001)

Finally, the smooth spline curve showed the association of hemoglobin drop and adjusted odds ratio for in-hospital mortality, which reflected the association of hemoglobin drop and in-hospital mortality (Figure 1).

Discussion

The salient point of our findings is the following: hemoglobin drop ≥3g/dL was associated with increased risk of in-hospital mortality and AKI.

Additionally, it has been shown that AKI is associated with higher hospital mortality and respiratory failure due to COVID-19 (22). Patients with endotracheal intubation were likely to have advanced stage of AKI (22). However, it remains uncertain what is the pathophysiology of AKI resulting into death. Our data suggested that hemoglobin drop was associated with AKI and in-hospital mortality. The combination of hemoglobin drop and AKI contributed to even worse in-hospital mortality compared to hemoglobin drop without AKI. That is a novel finding in terms of prognostication of patients with COVID-19.

The bleeding avoidance strategy is essential for patients with cardiovascular disease who need antiplatelet and anticoagulation therapy because it can prevent AKI and mortality (23, 24). According to our study, the same concept may be applied to the patients with COVID-19. Patients with COVID-19 needs steroid treatments and anticoagulation therapy as prophylactic or therapeutic (2, 25). Although proton pump inhibitor is not useful for patients in intensive care units (26), it may not be applicable to the patients with COVID-19 on steroids and anticoagulation. Interestingly, our data showed the association of hemoglobin drop with in-hospital outcomes, reflecting the importance of the trend of hemoglobin even though patients do not have obvious site of bleeding (27-29).

Whether to use prophylactic versus therapeutic anticoagulation therapy is still actively debated (2, 30-33). We illustrated hemoglobin drop was independently associated in-hospital outcomes including AKI and death despite of rigorous adjustment with prophylactic and therapeutic anticoagulation. As of May 27th, 2021, we have no clear answer which to use prophylactic and therapeutic anticoagulation for patients with COVID-19. Nevertheless, we might be able to choose prophylactic or therapeutic anticoagulation based on hemoglobin trend on the daily basis, unless patients have the indications of therapeutic anticoagulation such as atrial fibrillation or venous thromboembolism.

The association between anemia and outcomes in COVID-19 patients has been reported only in a few studies. In the retrospective study analyzing the association of anemia due to COVID-19 diagnosed within 24 hours of admission and defined as hemoglobin level of less than 12 g/dl in women and less than 13 g/dl in men, patients with anemia were older and had more comorbidities. In this study, the presence of anemia on admission was associated with a higher proportion of severe COVID-19 cases (34). On the contrary, the prospective study of a small number of patients demonstrated that anemia was not associated with severe COVID-19 disease or significant elevations in inflammatory biomarkers (35). These findings implicate that anemia among COVID-19 patients found on admission is representative of anemia due to chronic diseases and can be confounded by the duration of COVID-19 symptoms and the variable level of inflammatory response in each individual. Therefore, we consider hemoglobin drop that was observed during close monitoring in a hospital setting is more representative affecting mortality.

The direct causal relationship between hemoglobin drop and in-hospital mortality is still not conclusive. Low hemoglobin levels could decrease oxygen delivery causing poor tissue oxygenation. It has been shown that anemia is associated with cardiac injury demonstrated as higher NT-pro BNP and a higher proportion of patients with increased creatinine cases compared to non-anemic patients (34). Another possibility is that respiratory distress or increased work of breathing could have been triggered by increased cardiac workload due to hemoglobin drop, which led to endotracheal intubation. These peripheral organ injuries due to low hemoglobin and respiratory distress indirectly caused by hemoglobin drop are potential contributing factors to higher in-hospital mortality observed among COVID-19 patients.

Our study is not without limitations. This is a retrospective observational study and not a study to collect all variables prospectively. Despite multiple imputations for missing data and propensity score matching analysis, we could not exclude unmeasured confounders. We adjusted for treatments such as steroid, anticoagulation, interleukin-6 inhibitor and convalescent plasma and we assessed the outcomes with the well-balanced cohort. Finally, we do not have an outcome of bleeding.

In conclusions, hemoglobin drop during COVID-19 related hospitalization was associated with higher risk of in-hospital mortality and AKI.

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Study concept and design: TK

Data Curation: TK, MT, NE

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: TK

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Statistical analysis: TK, MT

Administrative, technical, or material support: NE

Study supervision: NE

Figure Legends

Figure 1:

Smooth spline curve of the association of hemoglobin drop and adjusted odds ratio of in-hospital mortality (X axis: hemoglobin drop [g/dL], Y axis: log of adjusted odds ratio of in-hospital mortality)

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Table 1: Baseline characteristics of patients admitted with COVID 19 stratified by hemoglobin drop

	Patients without hemoglobin drop N=5933	Patients with hemoglobin drop N=750	P value	SMD after IPTW
Age (years), mean(SD)	65.8 (16.2)	65.8 (16.9)	0.95	0.002
Male, n (%)	3315 (55.9)	428 (57.1)	0.56	0.073
Race, n (%)				
White	1647 (27.8)	195 (26.0)		
African	1349 (22.7)	200 (26.7)		
American	1545 (26.0)	186 (24.8)	0.035	0.072
Hispanic	362 (6.1)	31 (4.1)		
Asian	1030 (17.4)	138 (18.4)		
Other				
Length of stay (days), median [IQR]	7.22 [4.33, 12.73]	10.10 [6.35, 18.75]	<0.001	-
Number of Hemoglobin measurements, median [IQR]	7.00 [4.00, 11.00]	11.00 [7.00, 19.00]	<0.001	-
Comorbidities:				
Asthma, n (%)	349 (5.9)	27 (3.6)	0.013	0.031
COPD, n (%)	278 (4.7)	31 (4.1)	0.56	0.031
Hypertension, n (%)	2156 (36.3)	254 (33.9)	0.20	0.029
Diabetes mellitus, n (%)	1348 (22.7)	183 (24.4)	0.33	0.019
Obstructive sleep apnea, n(%)	154 (2.6)	12 (1.6)	0.127	0.046
Obesity, n (%)	558 (9.4)	49 (6.5)	0.012	0.055
HIV, n (%)	92 (1.6)	12 (1.6)	1.00	0.043

Cancer, n (%)	495 (8.3)	65 (8.7)	0.82	0.056
Atrial fibrillation, n (%)	474 (8.0)	63 (8.4)	0.75	0.021
Heart failure, n (%)	477 (8.0)	63 (8.4)	0.79	0.082
Coronary artery disease, n (%)	828 (14.0)	111 (14.8)	0.57	0.024
Peripheral artery disease, n (%)	255 (4.3)	33 (4.4)	0.97	0.033
Chronic viral hepatitis, n (%)	53 (0.9)	6 (0.8)	0.96	0.042
Alcoholic/non-alcoholic liver disease, n (%)	137 (2.3)	22 (2.9)	0.35	0.037
Vital signs:				
Temperature, median [IQR]	38.00 [37.39, 38.89]	38.39 [37.56, 39.22]	<0.001	0.12
Heart rate (/min), median [IQR]	94.0 [81.0, 107.0]	99.0 [84.0, 115.0]	<0.001	0.045
Respiratory rate (/min), median [IQR]	20.0 [18.0, 22.0]	20.0 [18.0, 24.0]	0.001	0.027
Systolic blood pressure (mmHg), median [IQR]	131.0 [117.0, 147.0]	129.0 [113.0, 146.0]	0.005	0.069
Diastolic blood Pressure (mmHg), median [IQR]	75.0 [67.0, 84.0]	76.0 [66.0, 85.0]	0.43	0.004
O_2 Saturation (%), median [IQR]	90.0 [84.0, 92.0]	85.0 [72.0, 91.0]	<0.001	0.12
Blood tests:				
White blood cell (K/μL), median [IQR]	7.10 [5.30, 9.70]	9.90 [6.80, 13.30]	<0.001	0.005
Hemoglobin (g/dL), median [IQR]	13.3 [12.0, 14.4]	14.2 [12.7, 15.5]	<0.001	0.089

Platelet (K/μL), median [IQR]	202.0 [154.0, 261.0]	217.0 [162.0, 287.0]	<0.001	0.051
eGFR (ml/min./1.73m^2), median [IQR]	71.5 [48.3, 95.2]	57.4 [30.9, 86.3]	<0.001	0.039
Blood urea nitrogen (mg/dL), median [IQR]	17.0 [12.0, 28.0]	26.0 [14.0, 48.0]	<0.001	0.053
Aspartate Aminotransferase, (U/L), median [IQR]	39.0 [27.0, 62.0]	46.0 [29.0, 79.0]	<0.001	-
Alanine Aminotransferase, (U/L), median [IQR]	29.0 [19.0, 49.0]	32.0 [20.0, 58.3]	0.001	-
C reactive protein (mg/L), median [IQR]	85.0 [38.4, 160.5]	120.9 [54.3, 211.4]	<0.001	-
D-Dimer (μg/mL), median [IQR]	1.23 [0.70, 2.23]	2.06 [1.04, 3.88]	<0.001	0.12
PT-INR, median [IQR]	1.10 [1.00, 1.20]	1.20 [1.00, 1.30]	<0.001	-
PTT, median [IQR]	32.2 [29.1, 36.3]	31.8 [28.6, 35.6]	0.035	-
Treatment:				
Therapeutic anticoagulation, n (%)	1432 (24.1)	231 (30.8)	<0.001	0.006
Prophylactic anticoagulation, n (%)	4475 (75.4)	505 (67.3)	<0.001	0.026
Steroid treatment, n (%)	3249 (54.8)	382 (50.9)	0.052	0.012
IL-6 inhibitor, n (%)	199 (3.4)	58 (7.7)	<0.001	0.092
Convalescent Plasma, n (%)	851 (14.3)	82 (10.9)	0.013	0.021
Remdesivir, n (%)	1257 (21.2)	74 (9.9)	<0.001	0.036
Transfusion, n (%)	171 (2.9)	88 (11.7)	<0.001	-

eGFR: estimated glomerular filtration rate, COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus, IL-6: interleukin-6, IQR: interquartile range, SD: standard deviation, SMD: standardized mean difference

Table 2: In-hospital outcomes of patients admitted with COVID 19 stratified by hemoglobin drop

	Patients without hemoglobin drop N=5933	Patients with hemoglobin drop N=750	P value
In-hospital mortality	1189 (20.0)	306 (40.8)	<0.001
Acute kidney injury			<0.001
No acute kidney injury	4506 (76.1)	362 (48.6)	
stage 1	563 (9.5)	102 (13.7)	
stage 2	166 (2.8)	45 (6.0)	
stage 3	686 (11.6)	236 (31.7)	
Liver injury	570 (9.6)	265 (35.3)	<0.001
Acute Venous Thromboembolism	63 (1.1)	13 (1.7)	0.15
Intensive care unit, n (%)	1027 (17.3)	336 (44.8)	<0.001
Endotracheal intubation, n (%)	570 (9.6)	265 (35.3)	<0.001

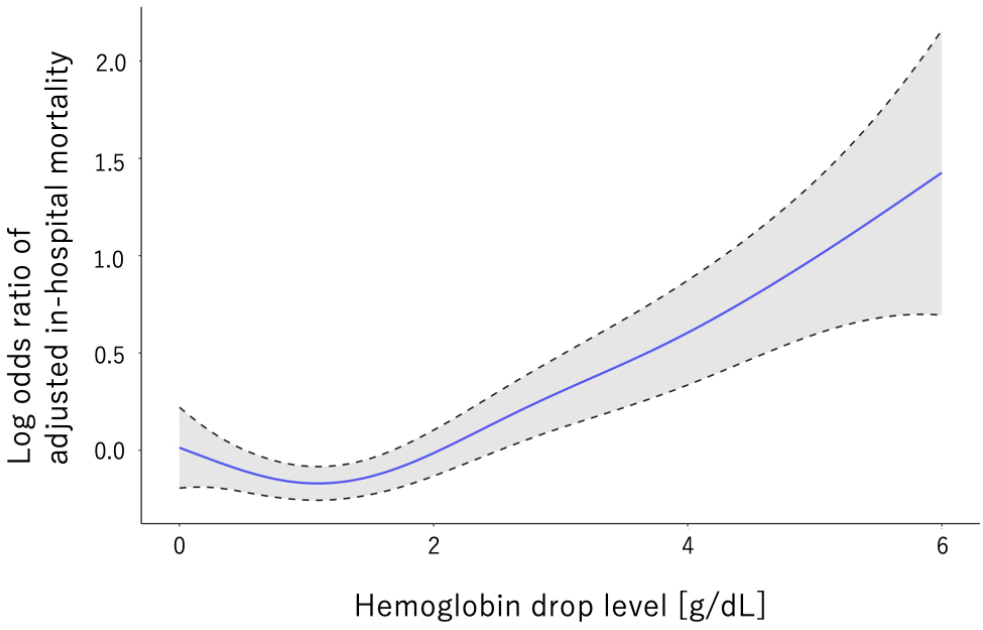

Figure 1

349x229mm (72 x 72 DPI)