Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short communication

Oxyhemoglobin concentrations do not support hemoglobinopathy in COVID-19

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ABSTRACT

Based on computerized modeling studies, it has been postulated that the severe hypoxemia in COVID-19 may result from impaired oxygen carrying capacity on hemoglobin. Standard pulse oximetry may not detect hypoxemia resulting from hemoglobinopathy, therefore hemoglobin co-oximetry is needed to evaluate this divergence. In a clinical data analysis of a multicenter cohort of hospitalized patients with COVID-19, we found a minimal effect, less than 1%, on the correlation between oxyhemoglobin concentration and predicted oxygen saturation in the presence of COVID-19 infection. This effect is unlikely to explain the clinically significant hypoxia in COVID-19 patients.

1. Introduction

The coronavirus 2019 disease (COVID-19) often presents with severe hypoxia, sometimes beyond that expected based on clinical symptoms and/or radiographic findings [1]. Based on computerized homology modeling studies, a widely circulated study by Liu and Li postulated that the severe hypoxemia may result from impaired oxygen carrying capacity on hemoglobin, due to direct binding by the virus to the beta chain and dissociation of iron from heme molecules [2]. A secondary analysis of that study found flawed interpretation of protein docking results [2,3]. Comparison of single-cell oxygen saturation imaging between 7 symptomatic COVID-19 patients and 3 asymptomatic controls also demonstrated no alteration in gas exchange [4].

Standard pulse oximetry may not detect hypoxemia resulting from hemoglobinopathy [5], therefore hemoglobin co-oximetry is needed to assess whether calculated oxygen saturations diverge from measured concentrations for a set partial pressure of oxygen (PO_2) value. A hemoglobinopathy induced by COVID-19 infection as postulated above should reduce measured oxyhemoglobin spectral proportion below expected based on oxygen tension [6]. Small clinical studies including a total of 67 patients have been published failing to demonstrate alterations in hemoglobin dissociation curves in critically ill patients based on diagnosis of COVID-19, but no larger cohorts have evaluated this effect [7,8]. Based on these smaller investigations, we analyzed clinical data for a multicenter cohort of hospitalized patients with COVID-19 to investigate the possibility of hemoglobinopathy-induced hypoxemia.

2. Methods

This study used data collected within the Mount Sinai Health System, a large urban hospital network comprising 8 medical centers throughout the New York City region. Cohort data was extracted from the Epic electronic health record (Verona, WI) using both Epic Caboodle and Epic Clarity databases. Patients were included in the cohort if they had an encounter diagnosis of COVID-19, an encounter with a COVID related visit type, a SARS-CoV-2 PCR lab order and/or result in Epic, a SARS-CoV-2 lab test result from New York State Department of Health or a positive COVID-19 antibody test. Only patients with both blood gas and COVID-19 PCR results were included in the analysis. Both arterial and venous samples processed either via central laboratory services or point-of-care testing were included in analysis. All blood gas specimens were analyzed at normalized temperature as per laboratory standard operating procedures using GEM 3000 and 5000 model analyzers (Werfen, Belgium) that use amperometric sensors for PO_2 detection and spectrometers for hemoglobin CO-Oximetry.

Viral PCR results were matched, one per patient encounter, to nearest blood gas values for the formation of matched pairs of laboratory tests for comparison. Pairs were excluded if time interval between PCR and blood gas result exceeded 24 h. Estimated saturation of oxygen (eSO_2) was calculated using the equation described by Severinghaus

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Table 1
Demographics and blood gases.

	COVID + (n = 1340)	COVID – (n = 10965)
Age (mean, SD)	67.6 (15.8)	61.3 (18.8)
% Female	52.3	54.0
pH (median, IQR)	7.40 (7.35–7.45)	7.39 (7.35–7.43)
pCO_2 (median, IQR)	38 (33–44)	41 (36–47)
pO_2 (median, IQR)	43 (32–59)	43 (33–63)
HCO_3- (median, IQR)	24.0 (20.9–27.0)	25.4 (22.4–27.9)
Oxyhemoglobin %	78.4 (62.1–90.4)	77.7 (62.1–91.1)
% In Emergency Department During Sample	13.4	25.3
% Encounter Required Intensive Care	25.6	27.9

(Eq. (1)), which depends only on the PO_2 [9].

$$eSO_2(\%) = \left(\frac{23400}{PO_2^3 + 150*PO_2} + 1\right)^{-1} *100 \quad (1)$$

Equation (1). Severinghaus Equation for Oxygen Saturation.

We employed multivariable linear regression to test the relationship between measured oxyhemoglobin absorption percentage with eSO_2 in the presence of COVID-19. Differences in pH, pCO_2, HCO_3, age, and gender were included as covariates, to adjust for possible confounding effects on oxygen carrying capacity. Bland-Altman plots were examined for differences between values based on mean saturation, and paired *t*-test and correlation testing based on these plots was performed according to COVID-19 diagnosis. Additional modelling restricted to patients with eSO_2 above 80% was performed to account for possible reduced accuracy of oxygen saturation calculation below this range [10]. All statistical analysis was carried out in SAS 9.4 (SAS Institute Inc, Cary, NC).

3. Results

Out of a total of 583,683 patient encounters in the health system COVID-19 registry, matched laboratory results were available for 9909 encounters (1.7%) in the final analysis, with 8764 unique patients. Laboratory results confirming COVID-19 were present in 10.8% (n = 1071) of the cohort. Demographics and raw blood gas data for COVID-19 positive and negative patients are presented in Table 1. Patients with COVID-19 were older than patients testing negative, with similar gender distribution. COVID-19 positive patients were less frequently in the Emergency Department during blood gas testing and had fewer admissions to Intensive Care during the encounter.

In the adjusted model, oxyhemoglobin percentages were highly predictive of eSO_2 values. The effect of COVID-19 positive testing reduced eSO_2 by 0.58% (95% CI 0.33%–0.83%) after correcting for other variables. Effect modification for COVID-19 PCR result on oxyhemoglobin association with eSO_2 ($p = 0.45$) was not present. The overall effect of COVID-19 PCR result remained significant when eSO_2 range was restricted to values > 80%, with a point estimate reduction of 0.54% (95% CI 0.35%–0.74%, $p < 0.001$). Age, but not gender, was significant in the adjusted model for prediction of eSO_2 values.

Visual inspection of Bland-Altman plots in the whole sample and in patients with $eSO_2 > 80\%$ (see Fig. 1) did not suggest bias based on COVID-19 diagnosis. Paired *t*-test analysis of differences of oxyhemoglobin concentration with eSO_2 suggest similar findings to our linear regression (difference 0.66, $p < 0.001$ for the entire group; difference 0.59, $p < 0.001$ for the group with $eSO_2 > 80\%$). Correlation was low for the association between difference in oxyhemoglobin concentration and eSO_2 in the entire cohort ($r = -0.056$, $p < 0.001$) but moderate in the sample with $eSO_2 > 80\%$ ($r = 0.331$, $p < 0.001$).

4. Discussion

Our analysis shows a minimal albeit significant effect on the correlation between measured oxyhemoglobin concentration on CO-oximetry and predicted oxygen saturation in the presence of COVID-19 infection. Given a magnitude of less than a single percentage point after controlling for other factors contributing to oxygen carrying capacity, this effect is unlikely to explain the clinically significant hypoxia in COVID-19 patients. Multiple other mechanisms have been proposed with supporting data which yield more substantial hypoxia, including pulmonary vascular dilation, pulmonary microthrombi, ventilation-perfusion mismatch, and pulmonary alveolar interstitial thickening [11,12]. Our

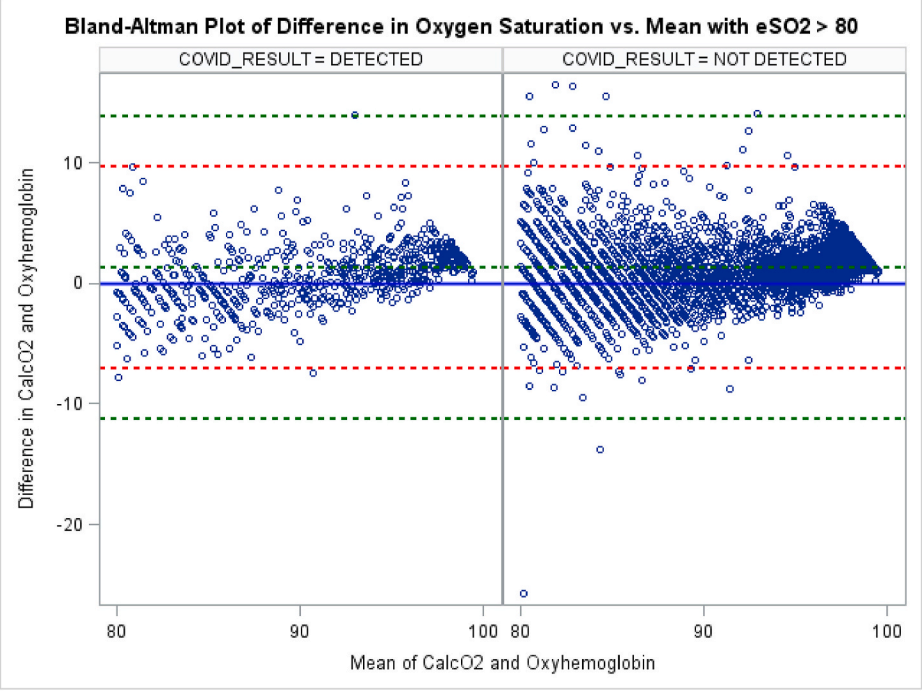

Fig. 1. Bland-Altman Plot for $eSO_2 > 80\%$.

findings support publications concluding that hemoglobinopathy unique to COVID-19 is unlikely [3,4,7,8].

Limitations of our analysis include the absence of clinical measurements of 2,3-diphosphoglyceric (DPG) concentrations, limited ability to account for hemoglobin concentration and patient temperature effects at time of sample acquisition. The significant association of age with saturation may indirectly reflect health conditions such as anemia, lung and cardiovascular conditions, and smoking prevalence which influence oxygen saturations.

We used only the nearest blood gas result to COVID-19 testing for each patient and did not track changes in oxyhemoglobin percentage over the disease course. Given possible decreased accuracy of the Severinghaus equation over lower PO_2 ranges [9], differences at low oxygen saturation ranges between groups may reflect confounding. Because cohort inclusion required at least one blood gas value, our population likely skews towards a sicker cohort of patients requiring higher levels of care.

Despite its preprint status, the Liu article has attracted numerous citations, nearly two million article views, and is listed as the top Altmetric article listed for ChemRxiv [2,3]. We have been unable to find any other published data supporting this hemoglobinopathy effect in COVID-19 disease. Given the lack of published evidence substantiating this mechanism, as well as our results above, we suggest that no clinically significant alteration of the hemoglobin oxygen carrying capacity exists in patients with COVID-19.

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CRediT authorship contribution statement

Patrick Maher: Conceptualization, Methodology, Writing – original draft. **Hamna Zafar:** Writing – review & editing. **Kusum Mathews:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors have no financial conflict of interest with the subject matter of this work.

References

[1] S. Richardson, J.S. Hirsch, M. Narasimhan, et al., Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area, J. Am. Med. Assoc. 323 (20) (2020) 2052–2059, https://doi.org/10.1001/jama.2020.6775.

[2] Liu W, Li H. COVID-19:Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. Published online July 13, 2020. doi: 10.26434/chemrxiv.11938173.v9.

[3] Read R. Flawed methods in "COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism." Published online May 5, 2020. doi:10.26434/chemrxiv.12120912.v2.

[4] Park KC, Donovan K, McKechnie S, Ramamurthy N, Klenerman P, Swietach P. Single-cell oxygen saturation imaging shows that gas exchange by red blood cells is not impaired in COVID-19 patients. *Br. J. Haematol.*. Published online August 1, 2020. doi:10.1111/bjh.17025.

[5] A. Jubran, Pulse oximetry, Intensive Care Med. 30 (11) (2004) 2017–2020, https://doi.org/10.1007/s00134-004-2399-x.

[6] M. Verhovsek, M.P.A. Henderson, G. Cox, H. Luo, M.H. Steinberg, D.H.K. Chui, Unexpectedly low pulse oximetry measurements associated with variant hemoglobins: a systematic review, Am. J. Hematol. 85 (11) (2010) 882–885, https://doi.org/10.1002/ajh.21810.

[7] Daniel Y, Hunt B, Retter A, et al. Haemoglobin oxygen affinity in patients with severe COVID-19 infection. *Br. J. Haematol.*. Published online May 26, 2020. doi: 10.1111/bjh.16888.

[8] A.W. DeMartino, J.J. Rose, M.B. Amdahl, et al., No evidence of hemoglobin damage by SARS-CoV-2 infection, Haematologica 105 (12) (2020) 2769–2773, https://doi.org/10.3324/haematol.2020.264267.

[9] J.W. Severinghaus, Simple, accurate equations for human blood O2 dissociation computations, J. Appl. Physiol. 46 (3) (1979) 599–602, https://doi.org/10.1152/jappl.1979.46.3.599.

[10] B.G. Carter, J.B. Carlin, J. Tibballs, H. Mead, M. Hochmann, A. Osborne, Accuracy of two pulse oximeters at low arterial hemoglobin-oxygen saturation, Crit. Care Med. 26 (6) (1998) 1128–1133, https://doi.org/10.1097/00003246-199806000-00040.

[11] A.S. Reynolds, A.G. Lee, J. Renz, et al., Pulmonary vascular dilatation detected by automated transcranial Doppler in COVID-19 pneumonia, Am. J. Respir. Crit. Care Med. 202 (7) (2020) 1037–1039, https://doi.org/10.1164/rccm.202006-2219LE.

[12] J. Herrmann, V. Mori, J.H.T. Bates, B. Suki, Modeling lung perfusion abnormalities to explain early COVID-19 hypoxemia, Nat. Commun. 11 (1) (2020) 4883, https://doi.org/10.1038/s41467-020-18672-6.