



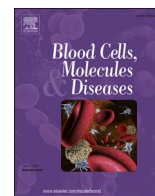
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

# Blood Cells, Molecules and Diseases

journal homepage: [www.elsevier.com/locate/bcmd](http://www.elsevier.com/locate/bcmd)

## Prognostic factors associated with COVID-19 related severity in sickle cell disease

Nalan Yurtsever<sup>a,\*</sup>, Vijay Nandi<sup>b</sup>, Yonah Ziemba<sup>a</sup>, Patricia A. Shi<sup>b,c,\*</sup>

<sup>a</sup> Department of Pathology, Zucker School of Medicine, Northwell Health, NY, United States of America

<sup>b</sup> Lindsley F. Kimball Research Institute, New York Blood Center, New York, NY, United States of America

<sup>c</sup> Department of Medicine, Division of Hematology-Oncology, Zucker School of Medicine, Northwell Health, NY, United States of America

### ARTICLE INFO

#### Keywords:

Sickle cell disease  
COVID-19  
Disease severity  
Prognostic risk

### ABSTRACT

**Background:** Equipose exists regarding sickle cell disease (SCD) as a risk factor for COVID-19 disease severity and variables that increase risk of COVID-19 severity in SCD. Given our health system's large SCD patient catchment, we analyzed our own experience in this regard.

**Study methods:** Retrospective analysis of the clinical course and factors associated with need for hospitalization and ICU admission of SCD patients diagnosed with COVID-19 through the Northwell Health system from March 1 to Dec 31, 2020.

**Results:** Of 1098 patients with SCD, 3.3% were diagnosed with COVID-19. Overall rates of hospitalization, ICU admission, cohort mortality, and in-hospital mortality were 80%, 19%, 2.5%, and 3.1%, respectively. By multi-variable analysis, hospitalization risk was decreased by 60% for every 1 g/dL increase in admission Hb. ICU admission risk was increased by 84% as a health care worker; increased by 45% for every 1000/uL increase in admission immature granulocyte count; and decreased by 17% with hydroxyurea use.

**Discussion:** High hospitalization rates are compatible with worsened severity upon COVID-19 infection in SCD compared to the general population. Patients should be placed on hydroxyurea to increase their Hb and perhaps lower their neutrophil counts. Health care workers with SCD may warrant special safety precautions.

### 1. Introduction

There is equipose as to whether sickle cell disease (SCD) is a risk factor for disease severity with COVID-19. Some studies support that SCD increases risk for COVID-19 disease severity [1–6], whereas other studies do not [7,8]. Despite possible increased COVID-19 disease severity in SCD, one large study did not show an increased fatality rate in SCD [4]. Patient variables associated with increased clinical severity of COVID-19 infection in SCD patients include older age [1,9], comorbidities [1,8–10], not being on hydroxyurea (HU) [1,9], history of stroke [2,8] and black race [5]. Non-SCD studies show similar risk factors such as older age [11,12], comorbidities [11,12], as well as being a health care worker (HCW) [13,14]. Possible laboratory-based predictors of hospitalization include the following admission values: high C-reactive protein (CRP) [1], low Hb [1,15,16], low lymphocyte count [1,15], high alanine aminotransferase [1], increased neutrophil-to-lymphocyte ratio [1,15], high immature granulocyte count (promyelocytes, myelocytes and metamyelocytes) [11,15,17], high creatinine [1], and high direct

bilirubin [1]. Possible in-hospital mortality values include high D-dimer [1,11], high creatinine levels [1,9,11], high lactate dehydrogenase [1,11], and high CRP [11] on admission. Fewer comorbidities may contribute to the better outcome of pediatric patients with COVID-19 infection [9]. In order to add our experience in the prognosis of SCD patients with COVID-19, we analyzed the clinical course and potential variables associated with need for hospitalization and ICU admission in all SCD patients diagnosed with COVID-19 infection throughout the Northwell Health system between March 1 and Dec 31, 2020.

### 2. Materials and methods

#### 2.1. Study

This study was conducted under institutional review board approval at Northwell Health.

\* Corresponding authors.

E-mail addresses: [nyurtsever@northwell.edu](mailto:nyurtsever@northwell.edu) (N. Yurtsever), [pshi@nybc.org](mailto:pshi@nybc.org) (P.A. Shi).

## 2.2. SCD patients

COVID-19 patients with SCD presenting between March 1 and Dec 31, 2020 were identified through Northwell's centralized electronic health record (EHR) system, which includes all patient data from 5 tertiary hospitals, 2 specialty hospitals and 7 community hospitals; this group includes the hospitals and their associated clinics caring for adult and pediatric SCD patients within the Northwell system as well as urgent care centers performing COVID-19 testing. The diagnosis of COVID-19 was determined by RT-PCR for SARS CoV-2 RNA on nasopharyngeal swab. The potential diagnosis of SCD was flagged by ICD-10 diagnosis or by a laboratory record of HbS  $\geq 35\%$ , and then confirmed by manual chart review to exclude the possibility of sickle cell trait. Northwell's overall catchment of unique SCD patients seen in 2020 was also enumerated through our EHR system using a HbS cutoff of  $\geq 60\%$  in order to exclude patients with sickle cell trait, and HbC and HbS each  $\geq 40\%$  to include Hb SC patients, as it was not feasible to manually review each patient record.

## 2.3. Retrospective chart review

Electronic and physical medical records of SCD patients with a diagnosis of COVID-19 were reviewed. Variables significant with previous publications or with scientific plausibility, and for which  $\leq 10\%$  of values were missing, were recorded for further analysis; they are listed in Supplementary Table 1. Lab values were defined as baseline when they were measured during steady state at a previous visit unrelated to the current or other acute illness, and defined as admission when measured in the emergency department or upon admission for hospitalized patients and at the emergency department visit for outpatients. Baseline severity of SCD was assigned a numeric score (between 0 and 1) based on a validated SCD severity scoring system [18] based on gender; sickle genotype; steady-state systolic blood pressure, bilirubin, lactate dehydrogenase (LDH), mean corpuscular volume (MCV), white blood cell and reticulocyte count; history within the past year of acute chest syndrome, vaso-occlusive crisis, and chronic transfusion; and lifetime history of priapism, stroke, avascular necrosis, and sepsis. Attribution of respiratory symptoms to COVID-19 versus SCD was determined by the hospital team; COVID-19 severity was graded using a 5-tier method based on degree of respiratory involvement: asymptomatic, mild, moderate, severe and critical [19];

## 2.4. Statistical analysis

R statistical software was used for all statistical analyses. Descriptive statistics were generated to characterize the study sample, non-parametric statistical tests were run for between-group comparisons, and logistic regression models were conducted for univariate and multivariable analyses. Due to our small sample size, a variable was considered for inclusion in the multivariable analysis (MVA) if on univariate analysis the p-value was  $p < 0.20$ , unadjusted for multiple comparisons. Also, since admission rather than baseline variables may be more easily obtainable in real-world scenarios, admission values were preferred for MVA if both p-values met the  $p < 0.20$  criteria. Finally, because multiple studies have looked at factors nonspecific to SCD that affect COVID-19 severity [12,15], more SCD-specific factors, such as sickle cell severity score versus aspartate aminotransferase (AST), were chosen for inclusion when the number of variables allowed in the MVA model was limited due to our small sample size. For the MVA, only variables with p-values  $< 0.05$  were considered significant.

## 3. Results

### 3.1. Sample statistics

Forty SCD patients (27 adults, 13 children) with COVID-19 were

identified. Our SCD catchment in the year 2020 was 1098 unique patients (578 adults, 520 children), translating to a symptomatic infection rate of 3.3% (36 symptomatic patients among 40; adult rate 4.7%, pediatric rate 2.5%). Patient characteristics are shown in Table 1, stratified by adult and pediatric groups. Of the 40 patients, 85% (23/27) of adults and 69% (9/13) of children were hospitalized; of the inpatients, 17% (4/23) adults and 22% (2/9) children went to the ICU. SCD severity scores were significantly lower in children compared to adults (mean  $0.06 \pm 0.05$  versus  $0.24 \pm 0.14$ , Wilcoxon rank sum test,  $p < 0.001$ ), with the Spearman correlation coefficient between age and SCD severity score being 0.84. Genotype distribution only in adults (45% SS, 33% SC, and 22% S $\beta$  thalassemia (5 S $\beta^0$  and 2 S $\beta^+$ )) differed significantly from the published population distribution of 75.6% SS, 17.8% SC, and 5.4% S $\beta$  (binomial exact test,  $p < 0.05$ ) [20]. Presenting symptoms were typical of SCD and/or COVID-19 infection and included fever, pain, shortness of breath and altered mental status. Of the 4 asymptomatic patients, the 3 adult inpatients (admitted for vaso-occlusive crisis) were tested per standard hospital admission protocol and the pediatric outpatient was tested due to known exposure to COVID-19.

### 3.2. Clinical course

Since COVID-19 infection may precipitate or exacerbate SCD-related complications [8,10,21], complications were classified as SCD-related or COVID-19-related as per Table 2; outpatients had no complications. Of the 15% (4 of 27) adults who experienced COVID-19 complications, all went to the ICU and required intubation, whereas no children had COVID-19 related complications. SCD-related complications were diagnosed in 52% (14) of adult and 38% (5) of pediatric patients (Fisher's exact test,  $p = 0.5$ ). The mortality rate for our SCD cohort with COVID-19 ( $n = 40$ ) was 2.5% (1 adult ICU patient) and the in-hospital mortality rate (hospitalized patients:  $n = 32$ ), was 3.1%. Hospitalization status was associated with both SCD-related and COVID-19 severity, with a strong association between hospitalization status and COVID-19 severity score (Fisher's exact test,  $p \leq 0.001$ ). Hospitalization status and ICU admission were therefore chosen as relevant outcomes for univariate and multivariable analysis; control groups were SCD patients with COVID-19 who were outpatients and floor inpatients, respectively.

### 3.3. Univariate and multivariable analysis

The p-values for the univariate analyses (UVA) of the two outcome measures are shown in Supplemental Table 1. Results of the MVA are shown in Table 3. For hospitalization status, the only significant variable was admission Hb (OR = 0.40, 95% CI: 0.15, 0.78): that is, every 1 g/dL increase in Hb decreased the odds of hospital admission by 60%. In hospitalized patients, ICU admission was associated with 3 variables: HU use, health care worker status and high immature granulocytes at admission. Using HU decreased the odds of ICU admission by 17% (odds ratio: 0.83, CI: 0.71–0.96). HU use was associated with higher HbF levels (mean  $\pm$  SD =  $10.6 \pm 6.1$  HU versus  $6.0 \pm 5.6$  no HU, Wilcoxon rank sum test  $p = 0.03$ , Supplemental Table 2), indicative of HU compliance. Being a health care worker increased the odds of ICU admission by 84% (odds ratio: 1.84, CI: 1.43–2.37). Every 1000/uL increase in the count of immature granulocytes increased the odds of ICU admission by 45% (odds ratio: 1.45, CI 1.32–1.59).

## 4. Discussion

Our study in SCD patients examined their rates of COVID-19 infection and related hospitalization, ICU admission, cohort mortality, and in-hospital mortality. We also performed a MVA of risk factors for COVID-19 related severity, as defined by need for hospitalization or ICU admission. Our symptomatic infection rate was 3.3%, compared to a symptomatic infection rate median of 8.6% in the general U.S. population [22]. Our data contrasts with a meta-analysis finding a higher

**Table 1**  
Overview of SCD patients with COVID-19 (n = 40)<sup>a</sup>.

		Inpatients (n = 32)				Outpatients (n = 8)	
		ICU (n = 6)		Floor (n = 26)			
		Adult (n = 4)	Peds (n = 2)	Adult (n = 19)	Peds (n = 7)	Adult (n = 4)	Peds (n = 4)
Mean age (SD)		45 (14.9)	9.5 (10.6)	39.4 (14.2)	10.1 (6.3)	32.0 (8.9)	14.8 (0.5)
% Female		75%	0%	63%	43%	100%	25%
Mean body mass index (SD)		21.4 (3.2)	14.8 (1.2)	25.9 (6.4)	20.2 (4.2)	24.6 (2.4)	23.6 (1.5)
Mean SCD severity score (SD)		0.33 (0.24)	0.12 (0.13)	0.23 (0.13)	0.05 (0.01)	0.17 (0.06)	0.06 (0.02)
% on hydroxyurea		25%	50%	74%	57%	None	50%
% healthcare worker		50%	None	5%	None	None	None
% black race		50%	50%	58%	86%	100%	100%
% sickle genotype		50% SS, 50% SC	100% SS	47% SS, 21% SC 21% Sβ <sup>0</sup> , 11% Sβ <sup>+</sup>	86% SS 14% SC	25% SS 75% SC	50%SS, 25% SC, 25% Sβ <sup>0</sup>
Comorbidities		% per category	Stroke: 25% Smoking: 25%	None	Hypertension: 16% Coronary artery disease: 5% Aortic coarctation: 5% Venous thrombosis: 21% Asthma: 16% Stroke: 11% Trigeminal neuralgia 5% Smoking: 11% End stage renal disease: 11% Systemic lupus: 5% HIV: 5%	Asthma: 29% Mitral valve replacement: 25%	Atrial tachycardia: 25% Asthma: 25% Stroke 25%
Presenting symptoms		Mean # (SD)	1 (0.5)	0 (0)	1 (0.9)	0.3 (0.5)	0.3 (0.4)
		% fever	75%	50%	26%	71%	75%
		% pain	50%	50%	74%	14%	25%
		% SOB	25%	none	42%	14%	25%
		% AMS	25%	none	11%	None	None
		Mean # (SD)	2 (0.8)	1 (0.0)	2 (0.7)	1 (0.5)	1 (0.8)
COVID-19 severity grade			100% critical	100% severe	16% asymptomatic 37% mild 37% moderate 10% severe	43% mild 28.5% moderate 28.5% severe	100% mild 25% asymptomatic 75% mild

<sup>a</sup> SD = standard deviation.

**Table 2**  
Patients with complications<sup>a</sup>.

		N	Floor (n=26)													ICU (n=6)								
			Adult (n=13/19)											Peds (n=3/7)		Adult (n=4/4)		Peds (n=2/2)						
<b>COVID-19 related complications</b>	Respiratory distress & intubation	4																x	x	x	x			
	Cardiomyopathy	1																					x	
	Pancreatitis	1																					x	
	Stroke	1																					x	
	Cytokine release syndrome	1																					x	
	Acute kidney injury	4		x																x		x	x	
	Pulmonary emboli	1		x																				
<b>SCD-related complications</b>	Acute pain episode	14	x	x	x	x	x	x	x	x	x	x	x	x								x	x	
	Acute chest syndrome	7			x									x	x								x	x
	Splenic complication <sup>‡</sup>	2																x						
		Priapism	1	x																				
<b>COVID-19 treatments</b>	Enoxaparin	7					x	x						x	x	x						x	x	
	Hydroxychloroquine	3																				x		
	Antibiotic	13	x	x		x								x	x							x	x	
	Remdesivir	3																					x	
	Steroid	2																					x	
		Anakinra	1																					
<b>SCD treatments</b>	Simple transfusion	14	x	x		x	x							x	x							x	x	
	Exchange transfusion	3																					x	
	Hydroxyurea (outpatient)	11	x	x	x																			
	Crizanlizumab (outpatient)	1																					x	
		L-glutamine (outpatient)	1																					x

The patient who died is highlighted in gray.

<sup>‡</sup> Sequestration in peds patient, infarct in adult patient.

<sup>a</sup> Each column represents an individual patient who experienced a complication (marked with an x).

**Table 3**  
Results of multivariable analyses.

Outcome	Parameter	Odds ratio	95% confidence interval	p-value
Hospital admission	Admission Hb (g/dL)	0.40	0.15, 0.78	0.026
ICU admission	Health care worker (yes/no)	1.84	1.43, 2.37	0.0001
	Hydroxyurea use (yes/no)	0.83	0.71, 0.96	0.017
	Admission immature granulocytes [K/ $\mu$ L]	1.45	1.32, 1.59	<0.0001

incidence of COVID-19 infection, but with a wide confidence interval, than in the general population [2], and may be related to our patients' compliance with COVID-19 mitigation measures such as social distancing (personal observation of one of our SCD physicians, Dr. Shi), as lack of access to care and testing is unlikely given that all patients included in the study had been seen in the year 2020. Interestingly, the sickle genotype distribution of our COVID-19 infected patients was significantly different from the SCD US population distribution [20]. This may be related to SARS-CoV-2 diagnostic bias toward symptomatic patients and is consistent with previous reports [5,21] of higher morbidity or mortality in the SC/S $\beta^+$  genotypes. Of note, as previously reported [1], our patients with SC/S $\beta^+$  genotypes were less likely to be on HU than SS/S $\beta^0$  genotypes (Fisher's exact test, p-value = 0.002). While our 19% ICU admission rate is similar to the U.S. general population rate [23], our 80% overall hospitalization is higher than the U.S. general population rate of 2% [22] but compatible with previously reported ranges in SCD between 41 and 76% for hospitalization and 11–20% for ICU [1,3–5,21]. Our higher-end hospitalization rate may reflect a conservative approach with our SCD patients. Also notable however, as reported previously [8,21], is that a majority of hospitalizations were for SCD-related rather than COVID-19 related complications, most frequently acute painful episodes. In fact, pediatric patients had no COVID-19 related complications, consistent with previously published milder courses in pediatric SCD patients [3,5,6,9]. Our cohort mortality of 2.5% is on the low end of the 3–10% range in SCD previously reported [1,4,5,21]; higher than the U.S. general population symptomatic fatality of 1.1% [22] but perhaps not higher when specifically compared to a U.S. black population [4,8]. Our in-hospital mortality rate of 3.1% was lower than the 8% found in a nearby geographic area [8] and again, may reflect a conservative approach to hospitalize our SCD patients.

In regard to risk factors for COVID-19 related severity, the only variable that held up to MVA for the outcome of hospitalization was admission Hb; this is consistent with previous findings of a significant Hb decrease from baseline for SCD patients requiring hospitalization [1] and studies that reported Hb as a strong predictor of COVID-19 related severity or mortality in the general population [16,24,25]. For the outcome of ICU admission, 3 variables remained significant in the MVA: HCW employment, HU use, and immature granulocyte count on admission. HCW employment has not been previously reported as a risk factor in SCD ICU admission but has been associated with COVID-19 morbidity in the general US population as well as comprehensive meta-analysis [13,14]. HU use has been reported to reduce morbidity in SCD in one report [1] but not others [10,21]. It is biologically plausible that HU might decrease morbidity from COVID-19 infection due to reduction of coagulation and neutrophil and endothelial cell activation [26–28]. Finally, the level of immature granulocytes has not been previously reported as a risk factor in SCD ICU admission, but is associated with disease severity and ICU admission in the general population [15,17].

In summary, our findings are compatible with SCD patients having more complications upon COVID-19 infection than the general population as measured by hospitalization rate. MVA suggests that patients

should be placed on hydroxyurea to increase their Hb and perhaps lower their neutrophil counts, and that health care workers with SCD may warrant special safety precautions. The advantage to our study is our thorough capture of all SCD patients across multiple sites of the largest health system in New York State diagnosed with COVID-19, in a state heavily affected by COVID-19 at the time and before COVID-19 vaccination became available. Nevertheless, our study is limited by its small sample size and its UVA and MVA limited to variables with  $\leq 10\%$  missing values.

## Declaration of competing interest

There are no conflicts of interest for any author.

## Acknowledgements

We thank our SCD patients who were the subjects of this study as well as the health care workers at Northwell Health who took care of them. Dr. Shi was supported by NHLBI PO1 HL149626.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bcmd.2021.102627>.

## References

- [1] C.P. Minniti, A.U. Zaidi, M. Nouraie, et al., Clinical predictors of poor outcomes in patients with sickle cell disease and COVID-19 infection, *Blood Adv.* 5 (1) (2021) 207–215, <https://doi.org/10.1182/bloodadvances.2020003456>.
- [2] S. Haghpanah, M. Hosseini-Bensenjan, M. Sayadi, M. Karimi, Incidence rate of COVID-19 infection in hemoglobinopathies: a systematic review and meta-analysis, *Hemoglobin* (2021) 1–9, <https://doi.org/10.1080/03630269.2021.1927751>.
- [3] T.S. Vilela, J.A.P. Braga, S.R. Loggetto, Hemoglobinopathy and pediatrics in the time of COVID-19, *Hematol. Transfus Cell Ther.* 43 (1) (2021) 87–100, <https://doi.org/10.1016/j.htct.2020.11.002>.
- [4] A. Singh, A.M. Brandow, J.A. Panepinto, COVID-19 in individuals with sickle cell disease/trait compared with other black individuals, *Blood Adv.* 5 (7) (2021) 1915–1921, <https://doi.org/10.1182/bloodadvances.2020003741>.
- [5] J.A. Panepinto, A. Brandow, L. Mucalo, et al., Coronavirus disease among persons with sickle cell disease, United States, March 20–May 21, 2020, *Emerg. Infect. Dis.* 26 (10) (2020) 2473–2476, <https://doi.org/10.3201/eid2610.202792>.
- [6] A.K. Clift, D. Saatci, C.A.C. Coupland, et al., Sickle cell disorders and severe COVID-19 outcomes: a cohort study, *Ann. Intern. Med.* (2021), <https://doi.org/10.7326/M21-1375>.
- [7] V. de Sanctis, D. Canatan, J.L.V. Corrons, et al., Preliminary data on COVID-19 in patients with hemoglobinopathies: a multicentre ICET-A study, *Mediterr. J. Hematol. Infect. Dis.* 12 (1) (2020), e2020046, <https://doi.org/10.4084/MJHID.2020.046>.
- [8] W.S. Hoogenboom, R. Fleysler, S. Soby, et al., *Haematologica* (2021), <https://doi.org/10.3324/haematol.2021.279222>.
- [9] B. Sayad, M. Karimi, Z. Rahimi, Sickle cell disease and COVID-19: susceptibility and severity, *Pediatr. Blood Cancer* 68 (8) (2021), e29075, <https://doi.org/10.1002/pbc.29075>.
- [10] L. Mucalo, A.M. Brandow, M. Dasgupta, et al., Comorbidities are risk factors for hospitalization and serious COVID-19 illness in children and adults with sickle cell disease, *Blood Adv.* 5 (13) (2021) 2717–2724, <https://doi.org/10.1182/bloodadvances.2021004288>.
- [11] B. Gallo Marin, G. Aghagholi, K. Lavine, et al., Predictors of COVID-19 severity: a literature review, *Rev. Med. Virol.* 31 (1) (2021) 1–10, <https://doi.org/10.1002/rmv.2146>.
- [12] I.J. Borges do Nascimento, N. Cacic, H.M. Abdulazeem, et al., Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis, *J Clin Med* 9 (4) (2020), <https://doi.org/10.3390/jcm9040941>.
- [13] S.A. Gomez-Ochoa, O.H. Franco, L.Z. Rojas, et al., COVID-19 in health-care workers: a living systematic review and meta-analysis of prevalence, risk factors, clinical characteristics, and outcomes, *Am. J. Epidemiol.* 190 (1) (2021) 161–175, <https://doi.org/10.1093/aje/kwaa191>.
- [14] A.K. Kambhampati, A.C. O'Halloran, M. Whitaker, et al., COVID-19-associated hospitalizations among health care personnel - COVID-NET, 13 states, March 1–May 31, 2020, *MMWR Morb. Mortal. Wkly Rep.* 69 (43) (2020) 1576–1583, <https://doi.org/10.15585/mmwr.mm6943e3>.
- [15] J. Linssen, A. Ermens, M. Berrevoets, et al., A novel haemocytometric COVID-19 prognostic score developed and validated in an observational multicentre European hospital-based study, *elife* 9 (2020), <https://doi.org/10.7554/elife.63195>.

- [16] D. Tremblay, J.L. Rapp, N. Alpert, et al., Mild anemia as a single independent predictor of mortality in patients with COVID-19, *EJHaem* (2021), <https://doi.org/10.1002/jha2.167>.
- [17] G. Carissimo, W. Xu, I. Kwok, et al., Whole blood immunophenotyping uncovers immature neutrophil-to-VD2 T-cell ratio as an early marker for severe COVID-19, *Nat. Commun.* 11 (1) (2020) 5243, <https://doi.org/10.1038/s41467-020-19080-6>.
- [18] P. Sebastiani, V.G. Nolan, C.T. Baldwin, et al., A network model to predict the risk of death in sickle cell disease, *Blood* 110 (7) (2007) 2727–2735, <https://doi.org/10.1182/blood-2007-04-084921>.
- [19] Y. Dong, X. Mo, Y. Hu, et al., Epidemiology of COVID-19 among children in China, *Pediatrics* 145 (6) (2020), <https://doi.org/10.1542/peds.2020-0702>.
- [20] S.L. Saraf, R.E. Molokie, M. Nouraie, et al., Differences in the clinical and genotypic presentation of sickle cell disease around the world, *Paediatr. Respir. Rev.* 15 (1) (2014) 4–12, <https://doi.org/10.1016/j.prrv.2013.11.003>.
- [21] J.B. Arlet, G. de Luna, D. Khimoud, et al., Prognosis of patients with sickle cell disease and COVID-19: a french experience, *Lancet Haematol.* 7 (9) (2020) e632–e634, [https://doi.org/10.1016/S2352-3026\(20\)30204-0](https://doi.org/10.1016/S2352-3026(20)30204-0).
- [22] F.J. Angulo, L. Finelli, D.L. Swerdlow, Estimation of US SARS-CoV-2 infections, symptomatic infections, hospitalizations, and deaths using seroprevalence surveys, *JAMA Netw. Open* 4 (1) (2021), e2033706, <https://doi.org/10.1001/jamanetworkopen.2020.33706>.
- [23] S. Garg, K. Patel, H. Pham, et al., Clinical trends among U.S. Adults hospitalized with COVID-19, March to December 2020: a cross-sectional study, *Ann. Intern. Med.* 174 (10) (2021) 1409–1419, <https://doi.org/10.7326/M21-1991>.
- [24] M. Al-Jarallah, R. Rajan, A.A. Saber, et al., In-hospital mortality in SARS-CoV-2 stratified by hemoglobin levels: a retrospective study, *EJHaem* (2021), <https://doi.org/10.1002/jha2.195>.
- [25] S.M. Oh, J.P. Skendelas, E. Macdonald, et al., On-admission anemia predicts mortality in COVID-19 patients: a single center, retrospective cohort study, *Am. J. Emerg. Med.* 48 (2021) 140–147, <https://doi.org/10.1016/j.ajem.2021.03.083>.
- [26] Y. Garnier, S. Ferdinand, M. Garnier, et al., Plasma microparticles of sickle patients during crisis or taking hydroxyurea modify endothelium inflammatory properties, *Blood* 136 (2) (2020) 247–256, <https://doi.org/10.1182/blood.2020004853>.
- [27] L. Elsherif, L.C. Scott, D. Wichlan, et al., Hydroxyurea therapy decreases coagulation and endothelial activation in sickle cell disease: a longitudinal study, *Br. J. Haematol.* 194 (3) (2021) e71–e73, <https://doi.org/10.1111/bjh.17650>.
- [28] A.M. Pedrosa, L. Leal, R.P.G. Lemes, Effects of hydroxyurea on cytotoxicity, inflammation and oxidative stress markers in neutrophils of patients with sickle cell anemia: dose-effect relationship, *Hematol. Transfus Cell Ther.* (2020), <https://doi.org/10.1016/j.htct.2020.07.011>.