Prognosis of patients with sickle cell disease and COVID-19: a French experience

Lancet Haematol 2020
Published Online
June 18, 2020
https://doi.org/10.1016/S2352-3026(20)30204-0

France is the country with the highest prevalence of sickle cell disease in Europe, with more than 26 000 patients diagnosed with the condition in 2018. Most of these patients are of sub-Saharan African origin.[1] Patients with sickle cell disease are thought to be at increased risk of COVID-19 complications. Aside from specific COVID-19-related morbidities, infections in patients with sickle cell disease[2] can provoke painful vaso-occlusive crisis and life-threatening acute chest syndrome. Thus, COVID-19 could be devastating for regions such as Africa or India, where an estimated 8–12 million patients with sickle cell disease live, or in the USA and Brazil, with more than 100 000 patients in each country.[3] Nevertheless, there are currently no data on the outcomes of patients with sickle cell disease and COVID-19.

On March 13, 2020, at an early stage of the COVID-19 pandemic in France, we invited all practitioners involved in the management of patients with sickle cell disease to report on all inpatients with sickle cell disease and confirmed COVID-19 by RNA detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from nasal swabs. An email was sent to paediatricians, internists, and haematologists involved in sickle cell disease managment in France by our national consortia —MCGRE (Filière de santé maladies constitutionnelles rares du globule rouge et de l'érythropoïèse) and Laboratory of Excellence GR-Ex network. We prospectively collected data on outcomes in patients with sickle cell disease infected with COVID-19 using a standardised form. We compared the prevalence of intensive care unit (ICU) admission for inpatients with sickle cell disease by age range to that of COVID-19-positive inpatients in France during the same period.[4] Data were collected between March 13, 2020, and April 16, 2020.

83 inpatients with sickle cell disease infected by SARS-CoV-2 from 24 centres were enrolled (table 1). The median age was 33·5 years (range 19–68) for the 66 (80%) adults and 12 years (0·3–17) for the 17 (20%) children (defined as patients <18 years). 48 (58%) of 83 patients had a past medical history of acute

	All patients (n=83)	Patients aged 0–14 years (n=12)	Patients aged 15–44 years (n=56)	Patients aged 45–64 years (n=14)	Patients aged 65–74 years (n=1)
Age	30 (0·3–68)	..	..	..	..
Sex					
Male	38 (46)	6 (50)	22 (39)	9 (64)	1 (100)
Female	45 (54)	6 (50)	34 (61)	5 (36)	0
Haemoglobin genotype					
SS/Sβ⁰	71 (86)	11 (92)	48 (86)	12 (86)	0
SC	8 (10)	0	5 (9)	2 (14)	1 (100)
Sβ⁺	4 (5)	1 (8)	3 (5)	0	0
Hydroxyurea treatment at admission	38 (46)	4 (33)	28 (50)	6 (43)	0
Hydroxyurea dose (mg/kg/day)	17·9 (8·8–30·2)	18·8 (18·6–23·3)	18·2 (11·8–30·2)	13·7 (8·8–16·5)	..
Weight (kg)	68 (5–110)	32 (5–49)	71·8 (41–110)	71·5 (59–95)	85
Vaso-occlusive crisis	44/81* (54)	6 (50)	34 (61)	4/12* (33)	0
Acute chest syndrome	23/82* (28)	2 (17)	17 (30)	4/13* (31)	0
Transfusion†	31 (37)	4 (33)	18 (32)	8 (57)	1 (100)
Length of hospital stay (days) ‡	8 (2–37)	4 (2–10)	7 (2–35)	10 (4–37)	22
Mechanical ventilation in the intensive care unit§	9/17 (53)	0	3/7 (43)	5/7 (71)	1 (100)

Data are n (%), n/N (%), or median (range). Percentages do not always equal 100% because of rounding. Ethnicity data were not collected in line with usual practice in France. *Data for vaso-occlusive crisis were not available for two patients and acute chest syndrome not available for one patient. †Simple transfusion or exchange transfusion (manual or automated) during the hospital stay. ‡Hospitalisation was completed for 80 (96%) of 83 patients and is ongoing at the date of the notification for the other three. §17 patients were admitted to the intensive care unit.

Table 1: **Patient characteristics by age range**

	Inpatients with sickle cell disease (n=83)		Hospitalised French population (n=17 745)*		p value†
	ICU admission	Deaths	ICU admission*	Deaths‡	
Age range (years)					
All patients	17 (20)	2 (2)	6075 (34)	2891/42 212 (7)	..
0–14	2/12 (17)	0	32/110 (29)	1/592 (<1)	0·72
15–44	7/56 (13)	0	514/2112 (24)	105/7524 (1)	0·039
45–64	7/14 (50)	2/14 (14)	3049/8422 (36)	1016/19 689 (5)	0·28
65–74	1/1 (100)	0	2480/7101 (35)	1769/14 405 (12)	..

Data are n (%) or n/N (%). *French general population younger than 75 years hospitalised with confirmed COVID-19 during the peak of the pandemic (April 7, 2020).[4] †Comparison of ICU admission prevalence by age range between inpatients with sickle cell disease and the French general population hospitalised with confirmed COVID-19 (Fisher's exact test). ‡Death prevalence by age range among all confirmed inpatients with COVID-19 younger than 75 years from March 1, 2020, to April 14, 2020, in France.[4]

Table 2: **ICU admission in patients with sickle cell disease and COVID-19**

chest syndrome, with a median of 2 episodes (range 1–10); 38 (46%) were being treated with hydroxyurea at admission (30 [51%] of 59 patients in the SS/Sβ⁰ subpopulation). Vaso-occlusive crisis was associated with COVID-19 in 44 (54%) of 81 inpatients and acute chest syndrome was associated with COVID-19 in 23 (28%) of 82 inpatients (table 1).

17 (20%) of 83 patients were admitted to the ICU. Nine (53%) required mechanical ventilation, including two patients treated with extracorporeal membrane oxygenation. Two patients died in the ICU with COVID-19 pneumopathy: two men with the SC haemoglobin genotype. Five (63%) of the 8 patients with the SC genotype were admitted to the ICU, compared with 12 (17 %) of 71 patients with the SS/Sβ⁰ genotype (p=0·0099 by Fisher's exact test). Among patients 40 years or older, 5 (31%) of 16 with the SS/Sβ⁰ genotype (median age 48·5 years, range 40–64) were admitted to the ICU versus five (100%) of five patients with the SC genotype (median age 50 years, 40–68; p=0·012). 15 (88%) of 17 patients with sickle cell disease admitted to the ICU were transfused with a median of 4 bags (range 2–7) of packed red blood cells per patient. Only 3 (20%) of 15 were transfused before ICU admission (1, 2, and 28 days before), and the other 12 were transfused after a median time of 1·5 days (range 0–9) after ICU admission. Two patients were treated with automated exchanges, 6 with simple transfusions, and 7 with exchange transfusions. One man with the SC genotype died 3 days after admission from a pulmonary embolism without transfusion, and a woman with the SS genotype was not transfused; instead she was treated with high-flow oxygen and then recovered. Of note, seven patients were directly admitted to the ICU; the median time to ICU transfer after hospital admission was 2 days (range 0–9).

Among patients with the SS/Sβ⁰ genotype, three (25%) of 12 received a transfusion before ICU admission, which was not different from the proportion of transfusions received throughout the stay for the 22 (37%) of 59 patients with the SS/Sβ⁰ genotype not requiring ICU admission. Treatment with hydroxyurea at admission was similar in both groups (six [50%] of 12 patients with the SS/Sβ⁰ genotype admitted to the ICU *vs* 30 [51%] of 59 patients with the SS/Sβ⁰ genotype not admitted to the ICU, median dose 16·7 mg/kg [range 8·8–22·7] *vs* 17·9 mg/kg [8·9–30·2]). Although these data are relatively few, they do not support an effect of transfusions or hydroxyurea for preventing ICU admission for the management of COVID-19 in patients with sickle cell disease.

The prevalence of ICU admission was significantly different between patients with sickle cell disease younger than 45 years and those 45 years or older; 9 (13%) of 68 patients with a median age of 28 years (range 0·3–44) versus eight (53%) of 15 patients with a median age of 54 years (45–68), p=0.0017. Compared with all other inpatients who tested positive for COVID-19 with the same age range, a biphasic trend was observed: a lower risk of ICU admission for young adults (15–44 years) with sickle cell disease than those without the condition (13% *vs* 24% admitted to ICU; odds ratio (OR) 0·44, 95% CI 0·16–0·99; p=0·039) and a higher but nonsignificant risk for older inpatients (45–64 years) with sickle cell disease (50% *vs* 36%; OR 1·76, 0·53–5·89; p=0·28, table 2). However, these data should be interpreted with caution because of a lack of statistical power to detect differences. A further limitation of this comparison is that the reasons for hospital admission in

the patients without sickle cell disease with COVID-19 could be different (eg, respiratory complaints) compared with patients with sickle cell disease, in part because of sickle cell disease-related complications (eg, vaso-occlusive crisis). Nevertheless, this bias should affect age groups similarly. Moreover, we confirmed that 30 (71%) of 42 patients with sickle cell disease in this study had findings of COVID-19 pneumonia on chest CT scans.

These results suggest that COVID-19, even if potentially severe, does not seem to carry an increased risk of morbidity or mortality in patients with sickle cell disease, as most patients worldwide have the SS/Sβ^0 genotype and are younger than 45 years. Our findings also suggest that vaso-occlusive crisis can complicate COVID-19 infection, occuring in around half of inpatients with sickle cell disease. The hypothesis of a protective effect against COVID-19 in patients with the SS/Sβ^0 variant should be explored. Patients with the SS genotype have been shown to have high plasma interferon-α concentrations and their neutrophils showed a clear type I interferon signature.[5] SARS-CoV-2 does not seem to trigger substantial interferon responses ex vivo, which could explain increased viral replication.[6] However, older patients with sickle cell disease should be considered vulnerable to SARS-CoV-2 and should follow guidelines from their respective country to prevent being exposed to it. These patients should also be closely monitored if they become hospitalised becasue of COVID-19.

We declare no competing interests.

*Jean-Benoît Arlet, Gonzalo de Luna, Djamal Khimoud, Marie-Hélène Odièvre, Mariane de Montalembert, Laure Joseph, Christelle Chantalat-Auger, Edouard Flamarion, Pablo Bartolucci, François Lionnet, Sebastien Monnier, Cécile Guillaumat, Aline Santin
jean-benoit.arlet@aphp.fr

French Sickle Cell Referral Centre, Department of Internal Medicine, Georges Pompidou European Hospital, AP-HP, 75015 Paris, France (J-BA, DK, EF); French Sickle Cell Referral Centre, Mondor Hospital, AP-HP, Creteil, France (GL, PB); Department of Paediatrics, Hôpital Armand Trousseau, APHP, Paris, France (M-HO); French Sickle Cell Referral Centre, Necker-Enfants malades Hospital, AP-HP, Paris, France (MM, LJ); French Sickle Cell Referral Centre, Bicètre Hospital, AP-HP, Paris, France (CC-A); Internal Medicine Department, Tenon Hospital, APHP, Paris, France (FL, AS); Internal medicine Department, Centre Hospitalier de Versailles, Versailles, France (SM); and Department of Paediatrics, Hôpital du Sud Francilien, Corbeil-Essonnes, France (CG)

1 Honsel V, Khimoud D, Ranque B, et al. Comparison between adult patients with sickle cell disease of sub-Saharan African origin born in metropolitan France and in sub-Saharan Africa. *J Clin Med* 2019; **8:** 2173.

2 Inusa B, Zuckerman M, Gadong N, et al. Pandemic influenza A (H1N1) virus infections in children with sickle cell disease. *Blood* 2010; **115:** 2329–30.

3 Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and interventions. *PLoS Med* 2013; **10:** e1001484.

4 Santé publique France. COVID-19: epidemiological update of April 9, 2020. April 9,2020. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-9-avril-2020 (accessed April 18, 2020).

5 Hermand P, Azouzi S, Gautier EF, et al. The proteome of neutrophils in sickle cell disease reveals an unexpected activation of interferon alpha signaling pathway. *Haematologica* 2020; published online March 5. DOI:10.3324/haematol.2019.238295.

6 Chu H, Chan JF, Wang Y, et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. *Clin Infect Dis* 2020; published online April 9. DOI:10.1093/cid/ciaa410.