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# Risk factors for severe COVID-19 in hospitalized sickle cell disease patients: A study of 319 patients in France

To the Editor:

Whether sickle cell disease (SCD) patients are at higher risk for severe COVID-19 and, among them, who are the most vulnerable is still a controversial issue. Indeed, fever or viral infections may trigger vaso-occlusive crisis (VOC) and consequently the need for hospitalization.[1] On the other hand, the tropism of SARS-CoV-2 in lung tissues and the increased risk of pulmonary embolism (PE) caused by this virus also raise questions in regards to SCD patients, in whom acute chest syndrome (ACS) is a leading cause of early mortality.[1,2]

In most studies of COVID-19 in SCD, the definition of "serious" or "severe" outcomes was particularly heterogenous. Here, we aimed to identify risk factors associated with mechanical ventilation and mortality in a large cohort of SCD inpatients.

From March 13, 2020 to May 15, 2021, all practitioners involved in SCD management in France, were contacted by our national consortia to consecutively reported SCD inpatients with confirmed SARS-CoV-2 infection (by RT-PCR testing from nasal swabs).[2] None of these patients had received COVID-19 vaccine in this period in France. Hospitalization related to COVID-19 was defined as confirmed or suspected COVID-19 as the reason for admission or admission within 14 days of a positive SARS-CoV-2 test result. Hospitalization was completed for all patients. This prospective, multicenter, observational cohort included the three predominant

genotypes responsible for SCD: Homozygous SS and compound heterozygous genotypes SC and Sβ-thalassemia. Anonymized data were collected by investigators using a standardized form with a minimal dataset. Data collected on past medical history were limited to ACS and three identified risk factors for COVID-19: hypertension, diabetes, and overweight. Concerning therapy at admission, collected data were immunosuppressive drugs, hydroxyurea, and date of the last red blood cell (RBC) transfusion program before hospitalization. The only recorded biological value was hemoglobin at admission.

Thromboembolism complications were declared by the investigator if confirmed by Doppler echography (for thrombophlebitis) or computed tomography (CT) pulmonary angiography (for PE). Nevertheless, no specific exam was systematically required.

When CT was performed and evaluated by a local radiologist at each center, the presence of ground grass opacities, at minimum, was considered to indicate COVID-19 pneumonia. ACS was adjudicated by investigators of each center based on respiratory symptoms and radiological findings (at minimum, new consolidation of a terminal segment in the lung bases). VOC was defined as bone pain not explained by causes other than SCD.

The cases of the first 83 patients in this database had been previously reported.[2]

Quantitative variables are expressed as the mean (standard deviation) or as the median (interquartile range). Between-group differences were evaluated using Student or a Mann–Whitney tests, as appropriate. Pearson's chi-square test was performed to illustrate the difference in proportions between groups (with Monte Carlo simulation if at least one count was <5). Logistic regression models were used to identify factors associated with our primary end point: The need for invasive mechanical ventilation or death. For multivariate analyses studying genotypes, imbalanced variables between groups were included as adjustment covariables. The level of significance was set at 5%. All statistical analyses were generated with R v3.6.0. This study was performed according to the principles of the Declaration of Helsinki.

Three hundred nineteen SCD patients (mean age 27.4 ± 14.4 years, 50.5% male) were hospitalized with confirmed COVID-19 in 36 centers in France; 27% were children (age < 18 years). Two hundred and seventy-six patients (86.5%) had the SS or $S\beta^0$ genotype and 33 (10.3%) the SC genotype (Table 1). Eighteen of the 319 inpatients (5.64%) died or required mechanical ventilation, all were adults. The case fatality rate was 2.2% in the whole population and 3% in adults ($n = 7$, 4 men). The median age at death was 50.4 years (range 36.4–85.4).

After adjusting for age, sex, genotype, weight, hydroxyurea use, and transfusion before hospitalization, multivariate analysis found that the SC genotype was a strong independent risk factor for mechanical ventilation or death (adjusted odds ratio (aOR): 6.99 [95% CI 1.42–34.5]; $p = .017$). Age was also an independent risk factor, with an aOR (per year increase) of 1.09 [1.04–1.14] (Figure S1).

None of the children or young adults younger than 20 years died or were intubated. In adults, SCD patients older than 40 years ($n = 59$) had an 8.3-fold increased risk [95% CI 2.6–31.2] of death or intubation compared to 20- to 40-year-old patients ($n = 153$) ($p < .001$) (Figure S2).

In the subset of $SS/S\beta^0$ inpatients ($n = 276$), risk factors for mechanical ventilation or death were older age, higher weight, hypertension, diabetes, and the use of steroid and immunosuppressive drugs (Table S1). Hydroxyurea use, chronic transfusion, or a recent RBC transfusion were not associated with a better outcome. In the subset of SC patients ($n = 33$), age was the only significant risk factor (Table S2).

Considering the unexpected severity in SC inpatients, we compared the characteristics of patients according to SCD genotypes (Table 1).

Eight of the 33 SC patients (24.2%) died or required mechanical ventilation, compared to 10 of the 276 (3.6%) $SS/S\beta^0$ patients ($p < .001$). The incidences of VOC, ACS, or confirmed COVID-19 pneumopathy during hospitalization were not different between groups. Interestingly, the incidence of all episodes of thrombosis was significantly higher in SC inpatients than in $SS/S\beta^0$ inpatients: 9/32 (28.1%) vs. 15/237 (6.3%), $p < .001$. Pulmonary embolism was the most frequent event, affecting 25% of SC inpatients and 5% of $SS/S\beta^0$ inpatients ($p < .001$). In multivariate analysis including age and weight, the SC genotype was the only independent factor associated with a higher risk of thrombosis (aOR = 5.86 [95% CI 1.59–21.59]) (Table S3).

In our large multicenter study, patients with the SC genotype appeared as a particularly high-risk group, with a case fatality rate of 12.1% in inpatients, compared to 1.1% in $SS/S\beta^0$ inpatients and 0% in $S\beta^+$ inpatients.

In the US, Panepinto et al. found increased mortality (more than a twofold increase) in $SC/S\beta^+$ genotypes compared to $SS/S\beta^0$ outpatients or inpatients with COVID-19.[3] The proportion of inpatients who required critical care was also higher in those with "mild" genotypes (8 of 29 [27.6%]) than in those with "severe genotypes" (7 of 99 [7.1%]) in a UK cohort.[4] In the latter, mortality was higher in those with "mild genotypes," although the differences did not reach significance. Patients with the SC and $S\beta^+$ genotypes were pooled in both those studies; however, as shown in our results, patients with the $S\beta^+$ do not appear to be a high-risk population. Moreover, the numbers of SC patients were low in these studies.

The specific vulnerability of patients with the SC genotype to severe outcomes of viral infection is a new and interesting finding. Indeed, it does not seem restricted to SARS-CoV-2 infection. Two retrospective studies, in French Caribbean territories ($n = 70$) and in Jamaica ($n = 40$) found that the SC genotype was significantly associated with severe dengue, with an increased mortality compared to SS patients.[5,6] Similar to SARS-CoV-2, dengue virus is known to have an endothelial tropism.[5,6] This raises questions about the specific vulnerability of SC patients to viruses that promote endothelial dysfunction.

Although the precise cause for this risk of severe outcome in SC inpatients infected by some viruses is unknown, our study offers a possible explanation. Indeed, the significantly higher prevalence of venous thromboembolism (VTE) events in SC inpatients than in SS inpatients, with identical VOC or ACS rates during hospitalization, is surprising. Blood viscosity is higher in SC patients than in SS patients and is considered to play a key role in the pathogenesis of some complications in SC patients, including an increased risk of VTE events.[7]

**TABLE 1** Characteristics on admission and complications during hospitalization of sickle cell disease inpatients infected by SARS-CoV-2 stratified by sickle cell genotype

| Variable | Total ($N = 319$) | SC (group 1) ($N = 33$) | SS + $S\beta^0$ (group 2) ($N = 276$) | $S\beta^+$ (group 3) ($N = 10$) | *p*-value group 1 vs 2 | *p*-value group 3 vs 2 |
|---|---|---|---|---|---|---|
| Age (years) | 26.2 [17.55–35.25] | 30 [22.1–40.3] | 26.1 [17.18–34.83] | 21.55 [18.92–37.68] | .104 | .909 |
| Sex (female) | 161/319 (50.47%) | 17/33 (51.52%) | 139/276 (50.36%) | 5/10 (50%) | 1.000 | 1.000 |
| Weight (kg) | 62 [50–73] | 72 [58–84] | 60 [49.35–71] | 70 [58–86] | .003 | .183 |
| Height (cm) | 168 [162–175], | 168 [163–174.25] | 168 [160.25–175] | 170 [164.75–182] | .816 | .364 |
| BMI (kg/m2) | 22 [19.28–25.1] | 24.15 [21.57–29.47] | 21.4 [19.1–24.5] | 23.35 [22.42–24.72] | .002 | .396 |
| Medical history of ACS | 178/308 (57.79%) | 11/33 (33.33%) | 164/265 (61.89%) | 3/10 (30%) | .003 | .052 |
| Number of ACS in the life | 2 [1–3] | 1 [1–1.5] | 2 [1–3] | 1 [1–3.5] | .006 | .628 |
| Arterial hypertension | 20/224 (8.93%) | 4/32 (12.50%) | 16/186 (8.60%) | 0/6 (0%) | .504 | 1.000 |
| Diabetes | 5/213 (2.35%) | 1/31 (3.23%) | 3/177 (1.69%) | 1/5 (20%) | 1.000 | .104 |
| Main symptoms on admission | | | | | | |
| >Fever | 136/255 (53.33%) | 11/29 (37.93%) | 121/220 (55%) | 4/6 (66.67%) | .125 | .692 |
| >Cough | 88/254 (34.65%) | 10/28 (35.71%) | 75/219 (34.25%) | 3/7 (42.86%) | 1.000 | .694 |
| >Dyspnea | 49/254 (19.29%) | 7/29 (24.14%) | 42/219 (19.18%) | 0/6 (0%) | .702 | .366 |
| >Oxygen saturation < 95% | 26/254 (10.24%) | 2/29 (6.90%) | 24/219 (10.96%) | 0/6 (0.00%) | .561 | .635 |
| Hemoglobin level on admission | 8.5 [7.6–9.55] | 9.95 [9.07–11] | 8.3 [7.2–9.3] | 9.4 [8.65–10.3] | <.001 | .035 |
| Treatment on admission | | | | | | |
| Hydroxyurea | 178/319 (55.80%) | 4/33 (12.12%) | 171/276 (61.96%) | 3/10 (30.00%) | <.001 | .051 |
| Hydroxyurea dose (mg/kg/day) | 18.8 [14.6–22.7] | 10.9 [8.98–12.1] | 18.8 [15.2–22.7] | 33.9 [27.6–40.2] | .003 | .114 |
| Exchange transfusion program | 41/315 (13.02%) | 0/33 (0%) | 41/272 (15.07%) | 0/10 (0%) | .027 | .370 |
| Transfusion 60 days before PCR | 42/319 (13.17%) | 2/33 (6.06%) | 39/276 (14.13%) | 1/10 (10%) | .276 | 1.000 |
| Delay (days) between last transfusion and PCR | 26 [17.75–35.75] | 37 [32.5–41.5] | 26 [18.5–35.5] | 17 [17–17] | .289 | .410 |
| Oral steroids[a] | 6/315 (1.90%) | 1/33 (3.03%) | 4/272 (1.47%) | 1/10 (10%) | 1.000 | .165 |
| Immunosuppressive drugs[b] | 8/317 (2.52%) | 1/33 (3.03%) | 7/274 (2.55%) | 0/10 (0.00%) | 1.000 | 1.000 |
| ACE inhibitors use | 25/298 (8.39%) | 4/33 (12.12%) | 21/255 (8.24%) | 0/10 (0%) | .504 | .616 |
| Complications and treatment during hospitalization | | | | | | |
| Mechanical ventilation or death | 18/319 (5.6%) | 8/33 (24.2%) | 10/276 (3.6%) | 0/10 (0%) | <.001 | 1.000 |
| Death | 7/319 (2.2%) | 4/33 (12.1%) | 3/276 (1.1%) | 0/10 (0%) | .003 | 1.000 |
| Thrombotic events | 24/278 (8.6%) | 9/32 (28.1%) | 15/237 (6.3%) | 0/9 (0%) | <.001 | 1.000 |
| >All venous thrombosis events | 23/278 (8.3%) | 9/32 (28.1%) | 14/237 (5.9%) | 0/9 (0%) | <.001 | 1.000 |
| >Pulmonary embolism | 20/279 (7.2%) | 8/32 (25%) | 12/238 (5%) | 0/9 (0%) | <.001 | 1.000 |
| >Other venous thrombosis | 5[c]/275 (1.8%) | 1/31 (3%) | 4/235 (1.7%) | 0/9 (0%) | .454 | 1.000 |
| >Arterial thrombosis event | 1[d]/277 (0.4%) | 0/32 (0%) | 1/236 (0.4%) | 0/9 (0%) | 1.000 | 1.000 |

**TABLE 1** (Continued)

| Variable | Total ($N = 319$) | SC (group 1) ($N = 33$) | SS + Sβ$^0$ (group 2) ($N = 276$) | Sβ$^+$ (group 3) ($N = 10$) | *p*-value group 1 vs 2 | *p*-value group 3 vs 2 |
|---|---|---|---|---|---|---|
| Painful vaso-occlusive crisis | 212/316 (67.1%) | 17/32 (53.1%) | 189/274 (69%) | 6/10 (60%) | .076 | .511 |
| Acute chest syndrome | 95/311 (30.5%) | 8/31 (25.8%) | 85/270 (31.5%) | 2/10 (20%) | .411 | .729 |
| Typical features of CT scan of COVID19 | 84/163 (51.5%) | 13/24 (54.2%) | 68/132 (51.5%) | 3/7 (42.9%) | .828 | .715 |
| ICU admission | 62/315 (19.7%) | 15/33 (45.5%) | 46/272 (16.9%) | 1/10 (10%) | <.001 | 1.000 |
| >Mechanical ventilation in ICU | 16/62 (25.81%) | 6/15 (40.00%) | 10/46 (21.74%) | 0/1 (0%) | .188 | 1.000 |
| >NIV or HFNC in ICU | 30/62 (48.39%) | 3/15 (20%) | 27/46 (58.7%) | 0/1 (0%) | .016 | .426 |
| >ECMO in ICU | 3/62 (4.84%) | 1/15 (6.7%) | 2/46 (4.3%) | 0/1 (0%) | 1.000 | 1.000 |
| ICU length of stay (days) | 6 [3.5–9] | 7 [4–9] | 5 [3.5–9] | 5 [5–5] | .522 | .931 |
| Hospitalization length of stay (days) | 7 [4–11] | 7 [6–15] | 7 [4–11] | 5.5 [4.25–8.5] | .109 | .407 |
| RBC transfusion | 120/315 (38.1%) | 12/33 (36.4%) | 107/272 (39.3%) | 1/10 (10%) | .851 | .095 |
| >Number of RBC bag | 2 [2–4] | 3 [2–5.5] | 2 [2–4] | 8 [8–8] | .167 | .107 |
| Specific treatment of COVID19 pneumonia[e] | 30/309 (9.7%) | 6/32 (18.7%) | 24/267 (9%) | 0/10 (0%) | .111 | 1.000 |

*Note*: Data are *n*/*N* (%), or median (interquartile range).

Abbreviations: ACE, Angiotensin-converting enzyme; ACS, acute chest syndrome; BMI, body mass index; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; ICU, intensive care unit; NIV, noninvasive ventilation; RBC, Red blood cell.

[a]Kidney transplant recipients ($n = 3$), systemic disease ($n = 3$).

[b]Tacrolimus ($n = 5$), methotrexate ($n = 3$), mycophenolate mofetil ($n = 3$), rituximab ($n = 1$) for kidney transplant recipients ($n = 3$) or systemic disease ($n = 5$).

[c]The 21 year-old SC patient, alive, had cerebral venous sinous thrombosis complicated by an ischemic stroke with hemiplegia; three SS patients had a catheter thrombosis (including two in ECMO circuit) and one SS a deep vein thrombosis.

[d]An ischemic stroke in a 31.5 years-old SS patient without past medical history of cerebral vasculopathy.

[e]Dexamethasone or tocilizumab.

Even significantly different between SS and SC genotypes (Table 1), Hb levels at admission were not different in SC patients with poor outcomes or thrombosis compared to other SC inpatients in our study, but we lack power in this subgroup of 33 patients (data not shown).

For the SS/Sbeta$^0$ subset of patients, more classic factors for severe COVID-19 were found. We emphasize that the cut-off age associated with a dramatic increase in poor outcomes was approximately 40 years, which was younger than that in the general population.

Sub-Saharan African countries have the highest prevalence of SCD worldwide, and some of them, have a very high prevalence of SC patients, up to 50% of SCD patients.[2] Most of these countries have lowest vaccines access. In that case, a priority of vaccination could be a focus on patients with the SC genotype and SS/S$\beta^0$ patients with comorbidities or older than 40 years.

The limitations of our study include the sparse data about organ complications, past history of VTE, socioeconomic factors, and biological or radiological findings during hospitalization. For example, we cannot rule out that a low glomerular fraction rate may contribute to worse outcomes, as creatinine was not collected. Conclusions regarding the association between SC genotype and more severe complications might also be limited by admission rate bias. Nevertheless, SC patients at the time of admission did not have a higher rate of respiratory symptoms, fever, or VOC than other genotypes.

Finally, in our study, an imaging examination was not systematically performed to screen the thrombotic events in all patients, but driven by clinical practice. It could underestimate the incidence of VTE events. However, this detection bias was normally identical in each group.

The main strengths of our study are the large number of patients identified, and the stringent definition of severe COVID-19.

In conclusion, SCD patients with the SC genotype admitted to the hospital with confirmed SARS-CoV-2 infection have poorer outcomes, with a higher prevalence of thromboembolism complications, than those with the SS/S$\beta^0$ genotypes.

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## CONFLICT OF INTEREST

All authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

Jean-Benoit Arlet conceived the study; contributed to patient recruitment; acquired, analyzed and interpreted the data; and wrote the manuscript. Djamal Khimoud contributed to the acquisition, analysis, and interpretation of data. Mariane de Montalembert, Marie-Hélène Odièvre, Laure Joseph, François Lionnet, Aline Santin, Emmanuelle Bernit, and Gonzalo De Luna contributed to patient recruitment; the acquisition, analysis, and interpretation of data; and manuscript preparation. Alain Garou, Giovanna Cannas, Pierre Cougoul, Corinne Guitton, Laurent Holvoet, Pablo Bartolucci, Geoffrey Cheminet, and Cécile Guillaumat contributed to patient recruitment and the acquisition and interpretation of data. All authors confirm that they had full access to all the data in the study.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

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# Venetoclax combined with FLAG-based chemotherapy induces an early and deep response in mixed-phenotype-acute leukemia

To the Editor:

Mixed-phenotype acute leukemia (MPAL) is a rare and heterogeneous group of malignant diseases, accounting for 2%–5% of acute leukemias. They are classified according to the European Group for Immunological Characterization of Leukemias, and the World Health Organization (WHO) as leukemia that expresses antigens of more than one lineage, myeloid (My), B or T lymphoid lineage, to such a degree that it is not possible to assign leukemia to a single lineage with certainty.[1] The genetic aberrations that drive MPAL remain largely unknown, with the exception of a small subset of MPALs harboring *BCR-ABL1* or *KMT2A* rearrangements. The diversity of phenotypes observed in MPAL may result from acquisition of mutations in a multipotent progenitor cell that primes leukemia cell for lineage promiscuity.[2] MPAL are high-risk diseases with a poor overall survival. In multivariate analysis, minimal residual disease (MRD) analysis therapy represents, as for other subtypes of acute leukemia, a major prognosis factor.

The choice of the induction chemotherapy regimen is not consensual due to the phenotypic heterogeneity of the disease. Most of the clinical data regarding response to treatment come from retrospective studies and case reports. The most widely used regimen is either acute myeloid leukemia (AML) or preferably acute lymphoid leukemia-based therapy.[3] However, it can lead to clonal expansion of blasts, which may resist the initial lineage-based chemotherapy.

FLAG-IDA induction including fludarabine (30 mg/m$^2$ D2–D6), cytarabine (2 g/m$^2$ D2–D6), idarubicin (6 mg/m$^2$ D2–D4), and filgrastim 5 μg/kg is an effective and well-tolerated induction chemotherapy, which provides high complete remission rates in newly diagnosed (ND) and relapsed/refractory (R/R) AML. Venetoclax (VEN) is a BCL-2 inhibitor, which has been approved in combination with hypomethylating agents (HA) or low-dose cytarabine for the treatment of ND AML in patients 75 years of age or older who are unfit for intensive induction chemotherapy. Venetoclax combined with HA improved patient-overall and event-free survival.[4] Previous studies reported in MPAL the efficacy of VEN in combination with HA.[5] For younger and fit patients with ND or R/R AML, adding VEN to FLAG-IDA recently showed impressive results,[6] suggesting a synergistic effect of VEN with intensive chemotherapy. MRD-negative composite CR was achieved in 96% of ND and 69% of R/R AML.

Here we present our findings in three patients with MPAL, who were treated with VEN combined with FLAG with or without idarubicin. We performed a retrospective review of single-center case series.

After patient informed consent, we extracted clinical, biological data from clinical records and analyzed flow cytometry data, to define patients fulfilling the criteria of MPAL according to WHO classification;[1] and significantly expressing BCL-2 (Figure 1). MPAL with t(9;22)(q34;q11.2) were excluded because other targeted treatments are available (tyrosine kinase inhibitors).

Three consecutive patients with MPAL were included between July 2020 and May 2021. Their median age was 43.9 years (19.8–53.3). One patient was in second relapse post-allogeneic transplant, and two were ND. Flow cytometry and immunohistochemistry analyses showed that the MPAL immunophenotype of the first patient was compatible with the rare B/T MPAL with positivity for CD19, CD7, CD33, cCD79a, cCD3, and TDT. MPO was negative. The second MPAL was a T/Myeloid MPAL