COVID-19 outcomes in patients with sickle cell disease and sickle cell trait compared with individuals without sickle cell disease or trait: a systematic review and meta-analysis

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Summary

Background Clinical manifestations and severity of SARS-CoV-2 infection in individuals with sickle cell disease (SCD) and sickle cell trait (SCT) are not well understood yet.

Methods We performed a systematic review and meta-analysis to assess COVID-19 outcomes in individuals with SCD or SCT compared to individuals without sickle cell disease or trait. An electronic search on PubMed, Embase, and Cochrane Library was performed on August 3, 2023. Two authors (IFM and ISP) independently screened (IFM and ISP) and extracted data (IFM and ILC) from included studies. Main exclusion criterion was the absence of the non-SCD/SCT group. Exposure effects for binary endpoints were compared using pooled odds ratio (OR) with 95% confidence intervals (CI). I^2 statistics was used to assess the heterogeneity and DerSimonian and Laird random-effects models were applied for all analyses to minimize the impact of differences in methods and outcomes definitions between studies. The overall quality of evidence was assessed using the GRADE system. Review Manager 5.4 and R software (v4.2.2) were used for statistical analyses. Registered with PROSPERO, CRD42022366015.

Findings Overall, 22 studies were included, with a total of 1892 individuals with SCD, 8677 individuals with SCT, and 1,653,369 individuals without SCD/SCT. No difference in all-cause mortality was seen between SCD/SCT and non-SCD/SCT (OR 1.18; 95% CI 0.78–1.77; p = 0.429; I^2 = 82%). When considering only studies adjusted for confounders (8 studies), patients with SCD/SCT were shown to be at increased risk of death (OR 1.86; 95% CI 1.30–2.66; p = 0.0007; I^2 = 34%). No significant difference was seen between individuals with SCD and SCT (p = 0.863). The adjusted for confounders analysis for hospitalisation revealed higher rates for the SCD (OR 5.44; 95% CI 1.55–19.13; p = 0.008; I^2 = 97%) and the SCT groups (OR 1.31; 95% CI 1.10–1.55; p = 0.002; I^2 = 0) compared to the non-SCD/SCT population. Moreover, it was significantly higher for the SCD group (test for subgroup difference; p = 0.028).

Interpretation Our findings suggest that patients with SCD or SCT may present with a higher mortality and hospitalisation rates due to COVID-19 infection.

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Research in context

Evidence before this study

There have been conflicting reports about whether sickle cell disease (SCD) or sickle cell trait (SCT) harbor a risk for worse outcomes in COVID-19. No meta-analysis comparing the outcomes of COVID-19 infection in individuals with SCD or SCT with individuals without SCD/SCT (e.g., general population) was found in a PubMed and Cochrane search for systematic review and meta-analysis in October of 2022. Therefore, we performed a systematic review and meta-analysis to assess the outcomes of COVID-19 infection in individuals with SCD or SCT compared to the general population. The first search using a combination of medical subject headings (MeSH) terms ("sickle cell disease"; "sickle cell trait" or "sickle cell disorders"; "COVID-19"; "SARS-CoV-2") was performed on October 24, 2022, and it was last updated on August 3, 2023. Only studies including a comparator group (individuals without SCD or SCT) were included. Studies comparing SCD or SCT with other hemoglobinopathies were excluded. Finally, 22 observational studies were included. Most of them (10/22) were considered of good quality. Eight were judged as being of fair quality and four of poor quality.

Added value of this study

To our knowledge, this is the first meta-analysis comparing COVID-19 outcomes in individuals with sickle cell disease or trait to the general population. Our findings suggest that patients with SCD or SCT and SARS-CoV-2 infection present with increased mortality rates compared to the general population. A separate analysis including only Black individuals with SCT sustained this result. Renal complications following COVID-19 infection may also more likely occur in individuals with SCT compared to individuals without SCD/SCT.

Implications of all the available evidence

Overall, our findings support that individual with SCD, SCT and SARS-CoV2-infection could be at higher risk of mortality than the general population. However, our meta-analysis was limited to observational studies, which decreases the level of certainty of our findings. Further research and ongoing collaborations are needed to better understand the complex interplay between SCD, SCT, and social determinants of health when evaluating vulnerabilities to emerging health threats.

Introduction

The wide spectrum of COVID-19 clinical manifestations is partially explained by certain demographic features and pre-existing medical conditions.[1] Older age, chronic lung disease, cardiovascular disease, cancer, chronic kidney disease, obesity, and transplantation are well-known risk factors associated with worse outcomes following SARS-CoV-2 infection.[1,2] However, there is still considerable uncertainty about whether certain specific conditions impact individuals' disease course.[1,2]

Sickle cell disease (SCD) is the most common monogenic disorder worldwide and is most prevalent in individuals with African ancestry.[3] In SCD, both copies of the beta-globin gene are altered (e.g., HbSS, HbSC, or HbS-β-thalassemia).[3] The sickle haemoglobin polymerises under hypoxic conditions, leading to a breadth of acute (e.g., vaso-occlusive crisis) and chronic complications, such as nephropathy.[3,4] During the H1N1 influenza pandemic, patients with SCD experienced increased rates of acute chest syndrome and intensive care unit admissions.[4,5] This raises concerns on how SARS-CoV-2 infection affects this population.

Sickle cell trait (SCT) refers to the heterozygous carrier state, meaning that the individuals harbour only one copy of the altered beta-globin gene (HbAS).[6,7] Individuals with SCT are considered mostly asymptomatic.[8] However, evidence suggests that under hypoxic conditions, subclinical sickling may occur.[7,8] This phenomenon could explain the observed increased risk of exercise-related injury and renal complications in the population with SCT.[7,8]

Nonetheless, there are divergent results in the literature on whether individuals with SCD and SCT are at higher risk of worse COVID-19 outcomes compared to the general population (e.g., individuals without SCD/SCT).[7,9–11] In fact, some studies suggest that individuals with SCD face a mild course of the disease and that it may be a protective factor against severe illness.[9,11]

Previous reviews have studied the interaction between hemoglobinopathies and COVID-19 infection and its clinical aspects.[6,12–15] A published meta-analysis has clarified some aspects regarding the incidence and mortality rates of COVID-19 in this population.[16] Yet, to our knowledge, no meta-analysis has studied the differences between individuals with SCD and SCT and those without SCD/SCT. In this meta-analysis, we seek to clarify the differences in outcomes of COVID-19 infection between individuals with SCD and SCT compared to the general population.

Methods

Study design

This systematic review and meta-analysis were performed according to the Cochrane Collaboration guidelines. Given the nature of this study, ethical

approval and participants' informed consent were not required. The manuscript was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[17] The study protocol was registered in October 2022 in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42022366015.

Search strategy and data extraction

A systematic search in the literature was performed from inception until October 24, 2022, in PubMed, Embase, and The Cochrane Library databases. The search was last updated in all databases on August 3, 2023. The following combination of medical subject headings (MeSH) terms was used ("sickle cell disease" or "sickle cell trait" or "sickle cell disorders" or "sickle cell anemia" or "hemoglobin S Disease" or "HbS Disease") and ("COVID-19" or "SARS-CoV-2" or "Severe Acute Respiratory Syndrome"). The search strategy was developed using keywords from previous reviews and MeSH terms and it was validated by an experienced librarian.[6,16] To assess its accuracy, it was validated using three studies that met the preliminary eligibility criteria. The full search strategy employed in the databases, along with the Boolean connectors and MeSH terms used can be found in the Supplementary Material (Table S1). References of all included studies as well as reviews were manually searched. Two authors (IFM and ISP) independently screened the articles using Zotero software (version 6.0.19). Two authors (IFM and ILC) independently extracted data from included studies. All inconsistencies between the authors were resolved by consensus or by consulting other authors (MV and SF).

Eligibility criteria

All original studies that compared outcomes of COVID-19 infection in patients with sickle cell disease or trait to a non-sickle cell disease or trait population (general population) were included. To be eligible for inclusion, studies were required to analyse at least one of the outcomes of interest described below. We included cross-sectional, retrospective cohorts, as well as case–control studies and studies reporting original data. Studies that utilised population-level databases, healthcare records or the International Classification of Diseases (ICD) for identifying sickle cell disease or trait and COVID-19 cases were considered for inclusion. Published abstracts from conferences were also included.

Case series without a comparator group, reviews, and letters to the editor were excluded, as well as manuscripts written in languages other than English. No restriction regarding the population size was made. Studies that compared SCD/SCT only with other blood disorders, that did not include a non-SCD/SCT group or did not investigate the outcomes of interest were also excluded. In studies with insufficient data, we tried to contact the authors to obtain the data.

Outcomes and subgroup analyses

The primary outcome of interest was all-cause mortality. Secondary outcomes included: (1) hospitalisation rate; (2) intensive care unit (ICU) admission; (3) respiratory failure or the need for invasive ventilation; (4) renal complications following COVID-19 infection; and (5) venous thromboembolism.

Because the definition of the primary outcome differed between studies, we have done a sensitivity analysis considering only studies reporting specifically COVID-19-related death,[7,18–20] which was described as any cause of death occurring up to 30 days of the COVID-19 diagnosis.[7,18,20] Respiratory failure and the need for invasive ventilation were considered in the same analysis. Invasive ventilation is here described as the need for mechanical ventilation. Renal complications include acute kidney failure (AKI) or renal failure (based on the need for new dialysis).

The mortality in Black individuals with SCT was investigated in a subgroup analysis. A subgroup analysis of the studies that performed adjusted analysis for confounding factors (namely, sex, age, weight or BMI, and comorbidities) was made for all the available outcomes (mortality, hospitalisation, ICU admission, and invasive ventilation). A separate analysis including only studies that performed adjusted analysis specifically for age was done to compare mortality rates in the SCD and SCT populations.

An exploratory analysis for sickle-cell disease-related complications (namely acute chest syndrome, vaso-occlusive crisis, and the need for transfusion) was performed, and COVID-19 clinical manifestations (pneumonia, dyspnoea, and fever) in the SCD group were assessed.

Statistical analysis

A comparative meta-analysis of exposure effects for binary endpoints using pooled odds ratio (OR) with 95% confidence intervals was conducted. I^2 statistics were used to assess the heterogeneity; I^2 >25% were considered appreciable for heterogeneity. Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to perform comparative analyses. Where the software only presented p-values to three decimal places, additional precision was obtained by transforming the test statistics to Z-values, and using these to compute p-values of the required precision.

Proportional meta-analysis was used to analyse the complications of SCD and COVID-19 outcomes in SCD patients. The pooled proportions were reported in percentages. Heterogeneity was explored using I^2 statistics cautiously since high heterogeneity may not mean data inconsistency in a proportional meta-analysis. High heterogeneity frequently happens in prevalence or incidence estimates due to the nature of the data and the

inherent differences among the populations of included studies.[21]

DerSimonian and Laird random-effects models were applied for all analyses. R Statistical Software (v4.2.2; R Core Team 2021) was used to run proportional meta-analysis, funnel plots, and Egger's Test.

Quality assessment

We have modified the Newcastle–Ottawa Scale for assessing the risk of bias in observational studies based on previous studies that adapted it to best suit their analysis.[22] The criteria used varied on the study design and are described in further detail in Supplementary Material Table S2. By this protocol, each study is classified as being of good, fair, or poor quality based on 3 items: selection of participants into the study, comparability of groups, and assessment of the outcome. Two authors (IFM and ILC) independently completed the risk of bias assessment. All inconsistencies between the authors were resolved by consensus and when this could not be reached, a third author (MV) was consulted. The overall quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and it was presented along with the summary of findings table (Supplementary Material Table S6).[23,24] Funnel plots of study weights versus point estimates, as well as the Egger test, were used to assess evidence of publication bias for the primary outcome (mortality).

Role of the funding source

There was no funding source for this study. All authors (IM, MV, ISP, ILC, CFL, MC, THT and SF) had access to the data presented in this study and accept responsibility for the decision of submitting it for publication. The final decision for submitting this study was made by IM, MV and SF.

Results

Initially, 1153 studies were identified through the electronic search. After the removal of duplicates and exclusion by title and abstract, 166 studies were included for a full review. Of these, 144 were excluded, mostly because of the design of the studies (not original studies), due to the absence of the non-SCD/SCT group, and lack of the outcomes of interest. A list of all excluded studies assessed can be found on the Supplementary Material (Table S4). Finally, 22 studies met our eligibility criteria and were included in our systematic review and meta-analysis (Fig. 1).[7,11,18–20,25–41]

Overall, a total of 1892 individuals with SCD, 8677 individuals with SCT, and 1,653,369 individuals without SCD/SCT, encompassing both the paediatric and non-paediatric population were included. The COVID-19 diagnosis was made mainly (14/22 studies) by polymerase chain reaction. Regarding sickle cell status, most studies (15/22) analysed SCD patients only (Table 1). Since sickle cell status (SCD versus SCT) was a subgroup analysis in a significant number of studies, detailed information regarding demographic characteristics and comorbidities for these subgroups was limited. Available information in each study, as well as the studies' outcomes that contributed to the meta-analysis, are summarised in Supplementary Material Table S5.

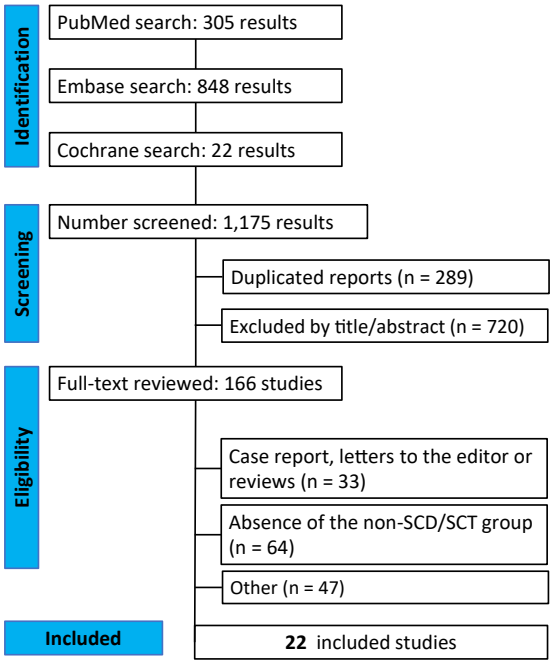

Fig. 1: PRISMA flow diagram of study screening and selection Legend: Blue vertical boxes indicate each stage of the screening process, and the horizontal boxes present more detailed information of the process, including the steps performed in each stage.

In some studies, we only obtained the odds ratio for a specific outcome. Therefore, the total number of patients accounting for each outcome could not be assessed in most analyses. The following analyses were initially planned but could not be made due to the unavailability of data or due to the lack of access to individual data: (1) renal complications in the SCD group; (2) mortality rate in Black individuals with SCD; (3) subgroup analyses according to haemoglobin genotype in the SCD population; (4) ICU admission for the SCT group; and (5) subgroup analyses in the paediatric population with SCD and SCT.

In the pooled analysis including 15 studies, we have found no significant difference in all-cause mortality between patients with SCD/SCT and those without SCD/SCT (OR 1.18; 95% CI 0.78–1.77, p = 0.429; I^2 = 82%) (Fig. 2). This finding was consolidated when analysing SCD (OR 1.12; 95% CI 0.59–2.14; p = 0.726; I^2 = 77%) and SCT subgroups (OR 1.26; 95% CI

Study	Study design	Location	Hospitalisation status	Age group	Sickle cell population	Number of patients with COVID-19 infection		Data source	Sickle cell status diagnostic method	COVID-19 diagnostic method
						SCD &/or SCT	Non-SCD/SCT			
Abdulrahman 2021[32]	Retrospective cohort	Bahrain	Hospitalised	NA	SCD	38	1754	Electronic medical records	Medical records[b]	PCR
Adamkiewicz 2021[33,a]	Retrospective cohort	United States	Hospitalised	Adult	SCD	48	2518	Electronic medical records	ICD-10	PCR
Alhumaid 2021[34]	Retrospective cohort	Saudi Arabia	Hospitalised	NA	SCD	31	983	Medical records	NA	NA
Arlet 2020[26]	Cross-sectional	France	Hospitalised	Adult and paediatric	SCD	83	17,745	Standardised form	NA	RNA detection
Boğa 2021[40]	Cross-sectional	Turkey	Hospitalised and non-hospitalised	Adult	SCD	39	121	Medical records	Medical records	PCR
Castonguay 2022[35]	Retrospective cohort	Canada	Hospitalised and non-hospitalised	Adult and paediatric	SCD	185	455,527	Standardised form	NA	PCR
Clift 2022[18]	Retrospective cohort	England	Hospitalised and non-hospitalised	Adult and paediatric	SCD and SCT	SCD: 287 SCT: 1346	541,460	QResearch database	ICD-10	NA
Foster 2020[27]	Retrospective cohort	United States	Hospitalised and non-hospitalised	Paediatric	SCD	4	53	Electronic medical records	NA	PCR
Goyal 2022[41,a]	Retrospective cohort	India	NA	NA	SCD	18	134	NA	NA	NA
Hoogenboom 2021[36]	Retrospective cohort	United States	Hospitalised	NA	SCD and SCT	SCD: 53 SCT: 62	12,544	Electronic medical records	ICD-10	PCR
Merz 2021[37]	Retrospective cohort	United States	Hospitalised	NA	SCT	20	146	Electronic medical records	HPLC	PCR
Mitchell 2020[38,a]	Retrospective cohort	United States	Hospitalised	Adult and paediatric	SCD	12	42	Medical records	NA	NA
Mucalo 2020[25,a]	Cross-sectional	United States	Hospitalised and non-hospitalised	Adult and paediatric	SCD	218	11,056	Standardised form	NA	NA
Nathan 2020[28]	Retrospective cohort	France	Hospitalised	Paediatric	SCD	3	20	Medical records	NA	PCR and/or typical aspects in CT
Paulukonis 2023[20]	Retrospective cohort	United States	Hospitalised and non-hospitalised	Paediatric	SCD and SCT	SCD: 387 SCT: 6426	389,865	MDSS and SendSS databases	Haemoglobin electrophoresis	PCR
Ramachandran 2020[11]	Retrospective cohort	United States	Hospitalised	Adult	SCD	9	53	Medical records	NA	PCR
Resurreccion 2021[39]	Retrospective cohort	United Kingdom	Hospitalised and non-hospitalised	Adult	SCT	21	7828	UKB database	ICD-10	NA
Shi 2022[29]	Cross-sectional	Scotland	Non-hospitalized	Paediatric	SCD	68	146,115	EAVE II database	Medical records	PCR
Singh 202[7]	Retrospective cohort	United States	Hospitalised and non-hospitalised	NA	SCD and SCT	SCD: 312 SCT: 449	45,517	TriNetX database	ICD-10	PCR
Van der Zalm 2021[30]	Retrospective cohort	South Africa	Hospitalised	Paediatric	SCD	1	158	Medical records	NA	PCR
Verma 2022[19]	Retrospective cohort	United States	Hospitalised and non-hospitalised	NA	SCT	353	13,488	MVP database	Directly genotyped or imputed markers in the haemoglobin beta gene	PCR
Ward 2022[31]	Retrospective cohort	England	Hospitalised	Paediatric	SCD	96	6242	NHS digital database	NA	NA

[a]Abstracts from conferences; SCD: sickle cell disease; SCT: sickle cell trait; NA: data not available; ICD-10: International Classification of Diseases, Tenth Revision. [b]In this study, the diagnosis of SCD was made through haemoglobin electrophoresis and confirmed by a positive sickling test result; PCR: Polymerase chain reaction; EAVE II: Early Pandemic Evaluation and Enhanced Surveillance of COVID-19; MVP: the Million Veteran Program; MDSS: Michigan Disease Surveillance System; SendSS: Georgia State Electronic Notifiable Disease Surveillance System; UKB: United Kingdom Biobank; HPLC: High-performance liquid chromatography.

Table 1: **Characteristics of studies included in the meta-analysis.**

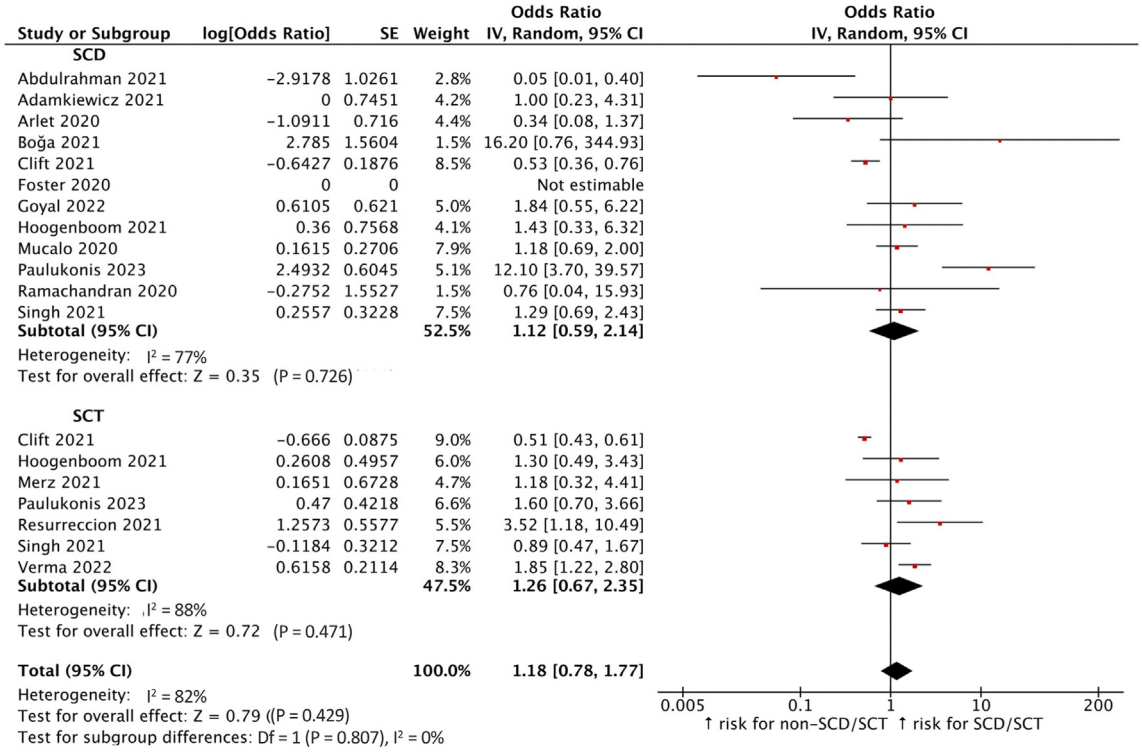

Fig. 2: All-cause mortality in the group with SCD and SCT groups not significantly different from the non-SCD/SCT group. Legend: Odds ratio for each trial are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects. The following studies analysed mortality in hospitalised patients: Abdulrahman 2021,[32] Adamkiewicz 2021,[33] Arlet 2020,[26] Hoogenboom 2021,[36] Ramachandran 2020,[11] and Merz 2021.[37] The following studies included both hospitalised and non-hospitalised patients: Boga 2021,[40] Clift 2022,[18] Foster 2020,[27] Mucalo 2020,[25] Singh 2021,[7] Resurreccion 2021,[39] Paulukonis 2023,[20] and Verma 2022.[19] For the study Paulukonis 2023 we used data from the population from Michigan.

0.67–2.35; p = 0.471; I^2 = 88%) separately and no difference was detected between them (p = 0.807) (Fig. 2). The sensitivity analysis including only studies assessing specifically COVID-19-related death have further confirmed these results (Supplementary material, Figure S1).

However, in the pooled analysis of eight studies adjusted for potential confounders, patients with SCD/SCT were found to be at increased risk of death (OR 1.86 95% CI 1.30–2.66; p = 0.0007, I^2 = 34%) compared with the population without SCD/SCT. In the subgroup analysis, a significant difference remained among individuals with SCT (OR 1.84 95% 1.32–2.56; p = 0.0003; I^2 = 0%), but not in the SCD group (OR 1.98 95% 0.94–4.15; p = 0.071; I^2 = 57%) (Fig. 3A). The test for subgroup difference was non-significant (p = 0.863) (Fig. 3A). We concluded that compared with patients who do not have SCD or SCT, the presence of either of these two conditions carries a similarly increased risk of mortality. We found similar results when analysing studies adjusted specifically for age (Fig. 3B). Moreover, the unadjusted for confounders analysis of three studies including 387 Black individuals with SCT demonstrated an increased mortality rate compared to Black individuals without SCD/SCT (OR 1.73; 95% CI 1.16–2.59; p = 0.007; I^2 = 0%) (Fig. 4).

An analysis of nine studies examining the hospitalisation rate in individuals with SCD revealed that this group presented with higher hospitalisation rates compared to individuals without SCD/SCT (OR 8.27; 95% CI 4.17–16.38; p < 0.0001; I^2 = 93%) (Supplementary Material, Figure S2). No increased risk for hospitalisation was observed for SCT when considering four studies assessing this outcome (OR 1.27; 95% CI 0.96–1.68; p = 0.095; I^2 = 82%) (Supplementary Material, Figure S2). A significant difference was assessed between individuals with SCD and SCT (p < 0.0001). The adjusted-for-confounders analysis of six studies revealed that individuals with SCT presented with increased hospitalisation rates compared to individuals without SCD/SCT (OR 1.31; 95% CI 1.10–1.55; p = 0.002; I^2 = 0%) (Supplementary Material Figure S3).

The meta-analysis comprising nine studies on the ICU admission in the SCD group revealed no significant difference between individuals with SCD and the

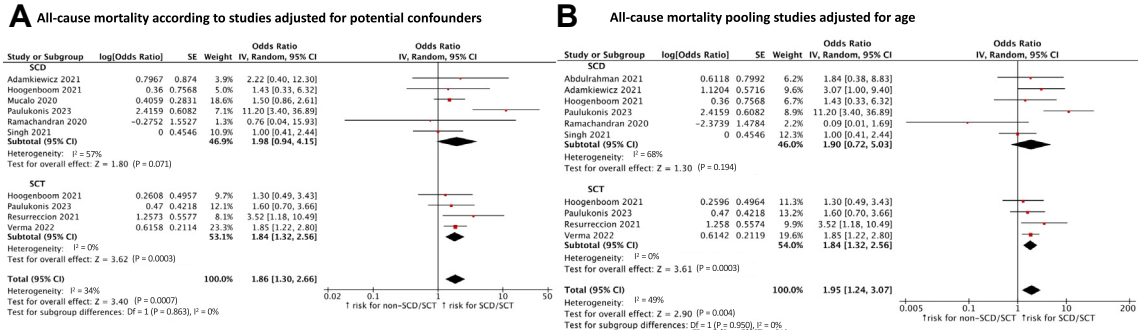

Fig. 3: All-cause mortality in individuals with SCD/SCT versus individuals without SCD/SCT according to studies adjusted for potential confounders (A), and for age (B) showing an increased risk of death for the population with SCD/SCT. (A) All-cause mortality according to studies adjusted for potential confounders (B) All-cause mortality pooling studies adjusted for age. Legend: Odds ratio for each trial are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects. For the study Paulukonis 2023 we used data from the population from Michigan.

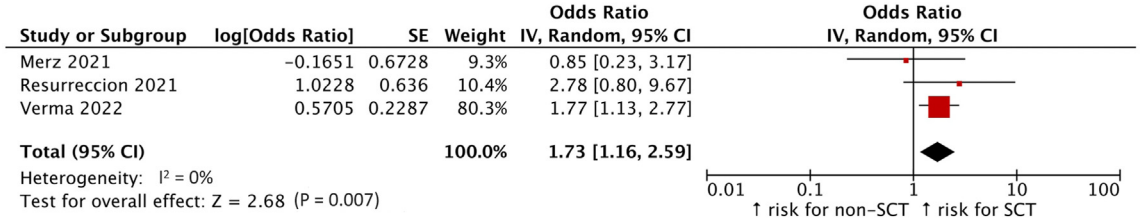

Fig. 4: Increased risk of death for Black individuals with SCT compared to Black individuals without SCD/SCT. Legend: Odds ratio for each trial are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects.

general population (OR 1.22; 95% CI 0.57–2.63; p = 0.603; I^2 = 81%) (Supplementary Material, Figure S4). This finding was confirmed in the analysis including four studies adjusted for confounders (OR 0.90; 95% CI 0.33–2.44; p = 0.843; I^2 = 57%) (Supplementary Material, Figure S5).

Regarding respiratory failure and the need for invasive ventilation, the analysis including nine studies revealed no significant differences between SCD and SCT groups and individuals without SCD/SCT (OR 1.17; 95% CI 0.75–1.82; p = 0.484; I^2 = 57%) (Supplementary Material, Figure S6). In the subgroup analysis of seven studies for the SCD and three studies for the SCT group, there was a non-significant trend of smaller risk for oxygen requirement in the SCT group (OR 0.70; 95% CI 0.49–1; p = 0.050; I^2 = 0%), but not for individuals with SCD (OR 1.46; 95% CI 0.88–2.41; p = 0.142; I^2 = 37%) (Subgroup comparison, p = 0.019). The respiratory failure or the need for invasive ventilation rate in individuals with SCD in four studies adjusted for confounding factors yielded similar results (OR 1.43; 95% CI 0.99–2.06; p = 0.059; I^2 = 0%) (Supplementary Material, Figure S7).

In an unadjusted for confounders analysis including three studies, the risk of renal complications was significantly higher in SCT patients (OR 1.61; 95% CI 1.14–2.26; p = 0.007; I^2 = 0%) following COVID-19 infection than in the non-SCT/SCD group (Fig. 5).

The exploratory analysis assessing the incidence of sickle cell-related complications following COVID-19 infection revealed that 24.2% (95% CI 12.1–38.8%) of SCD patients developed acute chest syndrome (Supplementary Material, Figure S8A). Vaso-occlusive crisis was reported in 23.1% (95% CI 11.0–42.1%) of patients (Supplementary Material, Figure S8B). Blood transfusion was needed in about 25% (95% CI 9.3–51.2%) (Supplementary Material, Figure S8C). We found pneumonia, dyspnoea, and fever occurring in 37.8% (95% CI 18.9–56.6%), 15.2% (95% CI 11.6–18.7%), and 47.4% (95% CI 27.5–67.3%) of patients, respectively (Supplementary Material, Figure S9A–C).

Overall, ten studies were considered of good quality.[7,18–20,25,26,29,35,36,39] Eight were judged as being of fair quality,[11,28,30–33,37,38] and four of poor quality (Supplementary Material, Figure S9).[27,34,40,41] Most of them included only hospitalised patients or did not perform adjusted analysis for confounders, therefore, failed to meet the necessary selection or comparability criteria to be considered of good quality (Supplementary

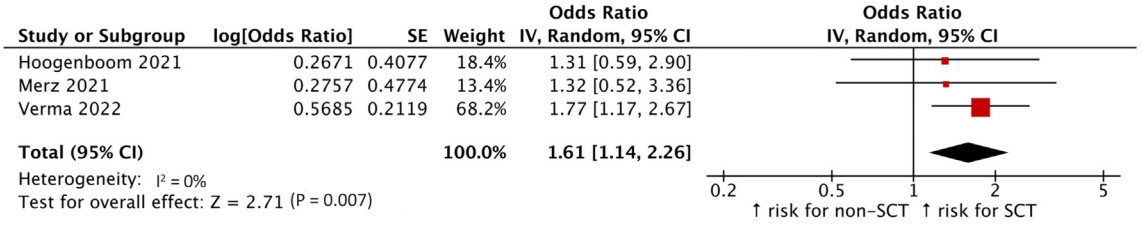

Fig. 5: Renal complications following COVID-19 infection were significantly more likely to occur in individuals with SCT compared to the control group. Legend: Odds ratio for each trial are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects.

Material, Table S3). On funnel plot analysis for all-cause mortality, an asymmetrical distribution of studies was seen for both SCD and SCT groups (Supplementary Material, Figure S10 A and B, respectively). The Egger's test did not suggest publication bias (z = 0.90; p = 0.39) for the SCD group and it was marginal for the SCT group (z = 2.66; p = 0.044). Of note, for the SCT group, the test was used in an analysis including only seven studies, which lowers its reliability and may therefore not reflect real asymmetry.

The certainty of evidence for mortality and renal complications was considered low by the GRADE assessment. The certainty of evidence for hospitalisation rate was considerate moderate since a large effect was detected. For ICU admission and respiratory failure, the certainty of evidence was classified as very low due to imprecision (Supplementary Material, Table S6).

Discussion

To our knowledge, this is the first meta-analysis assessing COVID-19 outcomes in the population with SCD or SCT compared to the general population. When considering only studies adjusted for potential confounders, we have found an increased mortality rate for the SCD/SCT group compared to the general population among studies adjusted for confounding factors, and no significant difference between the SCD and SCT subgroups. Higher hospitalisation rates were observed for the SCD and SCT populations. Increased mortality for Black individuals with SCT compared to other Black individuals without SCT/SCD was also seen in an unadjusted for confounders analysis including three studies.

There are divergent results in the literature on whether SCD adds additional risk for worse COVID-19 outcomes compared to the general population. A previous meta-analysis including 12 studies reported an increased rate of SARS-CoV-2 infection in the SCD population.[16] This study reported a slightly higher mortality rate in patients with hemoglobinopathies compared to the general population, consistent with our findings for individuals with SCD and SCT.[16]

In this meta-analysis, a surprising OR of 5.44 (95% CI 1.55–19.13) was observed in the adjusted for confounders analysis. The significantly higher hospitalisation rate in the SCD population is consistent with the previously published data.[7,18] A large study conducted in pre-pandemic periods using national data on emergency department visits by SCD patients in the United States estimated that almost 30% of these visits culminated in hospital admission.[42] In our study, sickle cell-related symptoms were registered in more than one-fourth of patients. Especially, vaso-occlusive crisis and acute chest syndrome constitute two of the most prevalent reasons for SCD patients' admission.[42] Hence, the SARS-CoV-2 infection may have substantially increased the incidence of SCD-related symptoms that culminated in hospital admission.

The complex and multifactorial pathophysiology of SCD relies on vaso-occlusion, and results in acute pain episodes.[3,35] As previously shown during the H1N1 pandemic, viral infections may enhance the inflammatory response already present in these patients, worsening sickle cell-related symptoms and resulting in severe illness.[3,4] It is reasonable to suggest that a similar response occurs following COVID-19 infection. Moreover, the adjusted for confounders analysis for both mortality and hospitalisation rates in the population with SCD suggests that SARS-CoV-2 severity can be attributed to SCD. The infection may affect individuals differently according to the genotype, with a possibly worse outcome of SC genotype compared to SS/Sbeta° genotypes.[26]

Interestingly, in our study, individuals with SCT had higher mortality and hospitalisation rates compared to individuals without SCD/SCT individuals. Due to the heterozygous haemoglobin state, sickle cell trait was thought to be a silent disease.[19,39] As pointed out by Verma et al. while national health agencies from different countries have emphasized the susceptibility of COVID-19 in patients with SCD, no specific recommendations were made to individuals with SCT.[19] Studies have shown that individuals with SCT are prone to develop organ dysfunctions, especially in the renal system, which is in agreement with our findings.[7,19] Furthermore, COVID-19 infection may lead to long-term complications.[19] Verma et al. reported that within 60 days of infection, individuals with SCT

experienced a significant incidence of AKI, accounting for nearly 21% of all COVID-19-related deaths.[19]

It is worth mentioning that only three of the included studies analysed renal abnormalities in the population with SCT.[19,36,37] Hoogenboom et al. and Verma et al. included analyses adjusted for differences in renal function between SCT and the control group.[19,36] On the other hand, no information regarding previous renal comorbidities in the SCT population was reported by Merz et al. except for increased levels of creatinine in individuals with SCT upon admission.[37] Considering this was the study with the smaller weight, no significant influence on the overall result is expected.

Few studies assessing viral infections in SCT individuals are available. A previous case report documented a potential association between H1N1 infection and AKI in a patient with SCT.[43] Kidneys have fewer oxygen reserves than other tissues and this state of low oxygenation may trigger sickling of the haemoglobin in the population with SCT and lead to renal abnormalities.[8,19] Due to the inflammatory process and the hypoxia that follows, COVID-19 infection could be an exacerbating factor in this scenario.[7,19] Whether the increased mortality observed in individuals with SCT and COVID-19 infection is related to renal complications remains uncertain. Thus, further research is warranted to better understand the clinical influence of SCT on COVID-19 outcomes.

The analysis including three studies for mortality rates in Black individuals with SCT showed increased rates for this subgroup compared to Black individuals without SCD/SCT. However, due to the unavailability of data from individuals' studies, we could not perform subgroup analyses stratified by race to truly understand its role in outcomes of individuals with SCT and COVID-19 infection. In addition, the confidence interval for this analysis was similar to the observed in the adjusted for confounders analysis for mortality. Therefore, this difference may have not been driven by race status but may only reflect increased mortality for individuals with SCT.

This study has some limitations. In some subgroup analyses including SCD and SCT, the control arm (individuals without SCD/SCT) may have included the same data for both SCD and SCT subanalyses. Since not all studies assessed the sickle cell status of the control group, it is possible that some individuals with SCT were included in the general population group. Considering the prevalence of SCT should not exceed more than 9% in the general population, we do not expect this to influence our results.[44] Due to the lack of access to SCD genotypes, it was not possible to assess the influence of the SCD genotype on COVID-19 clinical manifestations. Furthermore, in studies where sickle cell status was determined through ICD-10 coding, some individuals with SCT may have been misclassified as SCD.[45] Also, we did not have access to individual patient data. Thus, subgroup analysis in the paediatric and adult populations, as well as according to race, could not be made.

Other limitations include the differences in methods and some outcome definitions, which are reflected in significant heterogeneity observed in some analyses. To minimise these limitations, we have used strategies such as applying random-effects models in all analyses, conducting analysis based on outcome definitions, and including only studies adjusted for confounders. Additionally, in this meta-analysis, we could include only observational studies. Different designs and methodologies across them may have led to unidentified bias, thereby diminishing the certainty of our findings.

To our knowledge, this is the first meta-analysis assessing COVID-19 outcomes in SCD and SCT populations compared to individuals without SCT/SCD. The current data suggest that individuals with SCD and SCT had similarly increased COVID-19 mortality rates compared with individuals without SCD/SCT. Further research and ongoing collaborations are needed to better understand the complex interplay between SCD, SCT, and social determinants of health when evaluating vulnerabilities to emerging health threats.

Contributors

IM conceptualised the research question, performed the search in the databases, screened the studies, extracted data, performed the statistical analyses, and wrote the manuscript. MV assessed the statistical analyses, and provide insights on the methodology, data analysis and preparation of the manuscript. ISP screened the studies and reviewed the data. ILC extracted data and reviewed data. IM, ISP and ILC verified all data before final analyses. CFL assessed the conceptualisation process. CFL, MC, THT, and SF provided critical insight into the methodology, data analysis and preparation of the manuscript. SF assessed the conceptualisation process, statistical analyses, interpretation of data and preparation of the manuscript. All authors had full access to data in the study and had final responsibility for submitting it for publication.

Data sharing statement

All research data presented in this study is accessible upon request to the corresponding author.

Declaration of interests

The authors declare no conflict of interest that could potentially influence the findings presented in this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102330.

References

1 Gilyazova I, Timasheva Y, Karunas A, et al. COVID-19: mechanisms, risk factors, genetics, non-coding RNAs and neurologic impairments. *Noncoding RNA Res.* 2023;8(2):240–254. [cited 2023 Jun 22]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2468054023000082.

2 Manolis AS, Manolis AA, Manolis TA, Apostolaki NE, Melita H. COVID-19 infection and body weight: a deleterious liaison in a J-curve relationship. *Obes Res Clin Pract*. 2021;15(6):523–535. [cited 2023 May 31]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1871403X21001423.

3 Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. *Annu Rev Pathol Mech Dis*. 2019;14(1):263–292. [cited 2023 Apr 2]. Available from: https://www.annualreviews.org/doi/10.1146/annurev-pathmechdis-012418-012838.

4 Strouse JJ, Reller ME, Bundy DG, et al. Severe pandemic H1N1 and seasonal influenza in children and young adults with sickle cell disease. *Blood*. 2010;116(18):3431–3434. [cited 2023 Apr 2]. Available from: https://ashpublications.org/blood/article/116/18/3431/27913/Severe-pandemic-H1N1-and-seasonal-influenza-in.

5 George A, Benton J, Pratt J, et al. The impact of the 2009 H1N1 influenza pandemic on pediatric patients with sickle cell disease: H1N1 influenza and sickle cell disease. *Pediatr Blood Cancer*. 2011;57(4):648–653. [cited 2023 Apr 2]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/pbc.23030.

6 Hoogenboom WS, Alamuri TT, McMahon DM, Balanchivadze N, Dabak V, Mitchell WB, et al. Clinical outcomes of COVID-19 in patients with sickle cell disease and sickle cell trait: a critical appraisal of the literature. *Blood Rev*. 2022;53. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2015744015&from=export.

7 Singh A, Brandow AM, Panepinto JA. COVID-19 in individuals with sickle cell disease/trait compared with other Black individuals. *Blood Adv*. 2021;5(7):1915–1921. [cited 2023 Apr 2]. Available from: https://ashpublications.org/bloodadvances/article/5/7/1915/475624/COVID-19-in-individuals-with-sickle-cell-disease.

8 Naik RP, Haywood C. Sickle cell trait diagnosis: clinical and social implications. *Hematology*. 2015;2015(1):160–167. [cited 2023 Apr 2]. Available from: https://ashpublications.org/hematology/article/2015/1/160/20560/Sickle-cell-trait-diagnosis-clinical-and-social.

9 Bernit E, Romana M, Alexis-Fardini S, et al. Sickle cell disease patients with COVID-19 in guadeloupe: surprisingly favorable outcomes. *EJHaem*. 2022;3(3):636–643. [cited 2023 Apr 2]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jha2.449.

10 Minniti CP, Zaidi AU, Nouraie M, et al. Clinical predictors of poor outcomes in patients with sickle cell disease and COVID-19 infection. *Blood Adv*. 2021;5(1):207–215. [cited 2023 Apr 2]. Available from: https://ashpublications.org/bloodadvances/article/5/1/207/474881/Clinical-predictors-of-poor-outcomes-in-patients.

11 Ramachandran P, Perisetti A, Kathirvelu B, et al. Low morbidity and mortality with COVID-19 in sickle cell disease: a single center experience. *EJHaem*. 2020;1(2):608–614. [cited 2023 Apr 2]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jha2.87.

12 Lee JX, Chieng WK, Lau SCD, Tan CE. COVID-19 and hemoglobinopathies: a systematic review of clinical presentations, investigations, and outcomes. *Front Med*. 2021;8:757510 [cited 2023 Apr 2]. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.757510/full.

13 Pereira LRG, Da Silva MVG, Germano CMR, Estevao IF, Melo DG. Impact of the SARS-CoV-2 infection in individuals with sickle cell disease: an integrative review. *Front Med*. 2023;10:1144226 [cited 2023 May 31]. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2023.1144226/full.

14 Christian J, Lanzkron S, Naik RP. COVID-19 outcomes in sickle cell disease and sickle cell trait. *Best Pract Res Clin Haematol*. 2022;35(3):101382 [cited 2023 May 29]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1521692622000378.

15 Sayad B, Karimi M, Rahimi Z. Sickle cell disease and COVID-19: susceptibility and severity. *Pediatr Blood Cancer*. 2021;68(8) [cited 2023 May 29]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/pbc.29075.

16 Haghpanah S, Hosseini-Bensenjan M, Sayadi M, Karimi M. Incidence rate of COVID-19 infection in hemoglobinopathies: a systematic review and meta-analysis. *Hemoglobin*. 2021;45(6):371–379. [cited 2023 Apr 2]. Available from: https://www.tandfonline.com/doi/full/10.1080/03630269.2021.1927751.

17 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71 [cited 2023 Apr 2]. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.n71.

18 Clift AK, Saatci D, Coupland CAC, Dambha-Miller H, Hippisley-Cox J. Sickle cell disorders and severe COVID-19 outcomes: a cohort study. *Ann Intern Med*. 2021;174(10):1483–1487. [cited 2023 Apr 2]. Available from: https://www.acpjournals.org/doi/10.7326/M21-1375.

19 Verma A, Huffman JE, Gao L, et al. Association of kidney comorbidities and acute kidney failure with unfavorable outcomes after COVID-19 in individuals with the sickle cell trait. *JAMA Intern Med*. 2022;182(8):796 [cited 2023 Apr 2]. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2793722.

20 Paulukonis ST, Snyder A, Smeltzer MP, et al. COVID-19 infection and outcomes in newborn screening cohorts of sickle cell trait and sickle cell disease in Michigan and Georgia. *J Pediatr Hematol Oncol*. 2023;45(4):174–180. [cited 2023 Aug 15]. Available from: https://journals.lww.com/10.1097/MPH.0000000000002671.

21 Barker TH, Migliavaca CB, Stein C, et al. Conducting proportional meta-analysis in different types of systematic reviews: a guide for synthesisers of evidence. *BMC Med Res Methodol*. 2021;21(1):189 [cited 2023 Jun 25]. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-021-01381-z.

22 Wells G, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*; 2013. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

23 Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Available from: guidelinedevelopment.org/handbook.

24 *GRADEpro GDT: GRADEpro guideline development tool*. McMaster University and Evidence Prime; 2022. Available from: gradepro.org.

25 Mucalo L, Brandow AM, Dasgupta M, et al. Comorbidities are risk factors for hospitalization and serious COVID-19 illness in children and adults with sickle cell disease. *Blood Adv*. 2021;5(13):2717–2724. [cited 2023 Apr 2]. Available from: https://ashpublications.org/bloodadvances/article/5/13/2717/476266/Comorbidities-are-risk-factors-for-hospitalization.

26 Arlet JB, de Luna G, Khimoud D, et al. Prognosis of patients with sickle cell disease and COVID-19: a French experience. *Lancet Haematol*. 2020;7(9):e632–e634. [cited 2023 Apr 2]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2352302620302040.

27 Foster CE, Moulton EA, Munoz FM, et al. Coronavirus disease 2019 in children cared for at Texas children's hospital: initial clinical characteristics and outcomes. *J Pediatric Infect Dis Soc*. 2020;9(3):373–377. [cited 2023 Apr 2]. Available from: https://academic.oup.com/jpids/article/9/3/373/5854294.

28 Nathan N, Prevost B, Sileo C, et al. The wide spectrum of COVID-19 clinical presentation in children. *J Clin Med*. 2020;9(9):2950 [cited 2023 Apr 2]. Available from: https://www.mdpi.com/2077-0383/9/9/2950.

29 Shi T, Pan J, Moore E, et al. Risk of COVID-19 hospitalizations among school-aged children in Scotland: a national incident cohort study. *J Glob Health*. 2022;12:5044 [cited 2023 Apr 2]. Available from: https://jogh.org/2022/jogh-12-05044.

30 van der Zalm MM, Lishman J, Verhagen LM, et al. Clinical experience with severe acute respiratory syndrome coronavirus 2–related illness in children: hospital experience in cape town, South Africa. *Clin Infect Dis*. 2021;72(12):e938–e944. [cited 2023 Apr 2]. Available from: https://academic.oup.com/cid/article/72/12/e938/5973899.

31 Ward JL, Harwood R, Smith C, et al. Risk factors for PICU admission and death among children and young people hospitalized with COVID-19 and PIMS-TS in England during the first pandemic year. *Nat Med*. 2022;28(1):193–200. [cited 2023 Apr 2]. Available from: https://www.nature.com/articles/s41591-021-01627-9.

32 Abdulrahman A, Wael M, AlAmmadi F, et al. Is sickle cell disease a risk factor for severe COVID-19 outcomes in hospitalized patients? A multicenter national retrospective cohort study. *EJHaem*. 2021;2(2):167–174. [cited 2023 Apr 2]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jha2.170.

33 Adamkiewicz T, Mubasher M, Omole F, et al. Sickle cell disease (SCD) as a risk for COVI19 compared to those without SCD among patients admitted in a large urban center, as estimated by PCR sars-v-2 positive vs negative testing. *Blood*. 2021;138(Supplement 1):4170 [cited 2023 Apr 2]. Available from: https://ashpublications.org/blood/article/138/Supplement%201/4170/477650/Sickle-Cell-Disease-SCD-As-a-Risk-for-COVI19.

34 Alhumaid S, Al Mutair A, Al Alawi Z, et al. Clinical features and prognostic factors of intensive and non-intensive 1014 COVID-19 patients: an experience cohort from Alahsa, Saudi Arabia. *Eur J Med Res*. 2021;26(1):47 [cited 2023 Apr 2]. Available from: https://

eurjmedres.biomedcentral.com/articles/10.1186/s40001-021-00517-7.
35 Castonguay M, Dakhallah N, Desroches J, et al. COVID-19 and sickle cell disease in the province of quebec, Canada: outcomes after two years of the pandemic. *J Clin Med*. 2022;11(24):7361 [cited 2023 Apr 3]. Available from: https://www.mdpi.com/2077-0383/11/24/7361.
36 Hoogenboom WS, Fleysher R, Soby S, et al. Individuals with sickle cell disease and sickle cell trait demonstrate no increase in mortality or critical illness from COVID-19 - a fifteen hospital observational study in the Bronx, New York. *Haematologica*. 2021;106(11):3014–3016. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2015473897&from=export.
37 Merz LE, Mistry K, Neuberg D, et al. Impact of sickle cell trait on morbidity and mortality from SARS-CoV-2 infection. *Blood Adv*. 2021;5(18):3690–3693. [cited 2023 Apr 2]. Available from: https://ashpublications.org/bloodadvances/article/5/18/3690/476987/Impact-of-sickle-cell-trait-on-morbidity-and.
38 Mitchell WB, Davila JG, Keenan J, et al. Children and young adults admitted to a NYC children's hospital had a similar rate of severe COVID-19 coagulopathy as that reported in older adults. *Blood*. 2020;136(Supplement 1):27–28. [cited 2023 Apr 2]. Available from: https://ashpublications.org/blood/article/136/Supplement%201/27/470683/Children-and-Young-Adults-Admitted-to-a-NYC.
39 Resurreccion WK, Hulsizer J, Shi Z, et al. Association of sickle cell trait with risk and mortality of COVID-19: results from the United Kingdom Biobank. *Am J Trop Med Hyg*. 2021;105(2):368–371. [cited 2023 Apr 2]. Available from: https://www.ajtmh.org/view/journals/tpmd/105/2/article-p368.xml.
40 Boğa C, Asma S, Leblebisatan G, et al. Comparison of the clinical course of COVID-19 infection in sickle cell disease patients with healthcare professionals. *Ann Hematol*. 2021;100(9):2195–2202. [cited 2023 Apr 2]. Available from: https://link.springer.com/10.1007/s00277-021-04549-1.
41 Goyal V, Singh A, Memon Y, Thakre N, Sahu P, Goyal R. Sickle cell disease is a risk factor for the progression and prognosis of COVID-19. *HemaSphere*. 2022;6(3). Available from: https://journals.lww.com/hemasphere/pages/default.aspx.
42 Yusuf HR, Atrash HK, Grosse SD, Parker CS, Grant AM. Emergency department visits made by patients with sickle cell disease. *Am J Prev Med*. 2010;38(4):S536–S541. [cited 2023 Apr 3]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0749379710000024.
43 Bamber H, Rudge B, Vercueil A. An elevated creatine kinase in the context of influenza a infection and sickle cell trait. *Anaesth Rep*. 2019;7(1):57–59. [cited 2023 Jun 20]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/anr3.12017.
44 Ashorobi D, Ramsey A, Yarrarapu SN S, Bhatt R. *Sickle cell trait*. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537130/.
45 Reeves SL, Madden B, Wu M, et al. Performance of ICD-10-CM diagnosis codes for identifying children with Sickle Cell Anemia. Available from: *Health Serv Res*. 2020;55(2):310–317 [cited 2023 May 31] https://onlinelibrary.wiley.com/doi/10.1111/1475-6773.13257.