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REVIEW

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# The association of sickle cell disorder with adverse outcomes in COVID-19 patients: A meta-analysis

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## Abstract

The aim is to elucidate the relationship between sickle cell disorder and severe COVID-19. We systematically searched the required articles in three electronic databases, extracting and pooling effect sizes (ES) and 95% confidence interval (CI) from each eligible study to evaluate the effect of combined sickle cell disorder on adverse consequences in patients with COVID-19. This meta-analysis included 21 studies. Sickle cell disease (SCD) was a risk factor for mortality (pooled ES = 1.70, 95% CI: 1.00–2.92, $p = 0.001$), hospitalization (pooled ES = 6.21, 95% CI: 3.60–10.70, $p = 0.000$) and intensive care unit (ICU) admission (pooled ES = 2.29, 95% CI: 1.61–3.24, $p = 0.099$) in COVID-19 patients. Patients with SCD had an increased risk of respiratory failure/mechanical ventilation, but a statistical association was not found (pooled ES = 1.21, 95%CI: 0.74-1.98, $p = 0.036$). There was significant heterogeneity between SCD and death, hospitalization, and respiratory failure/mechanical ventilation. The results of meta-regression of SCD and hospitalization suggested that the tested variables including Area ($p = 0.642$), study design ($p = 0.739$), sample size ($p = 0.397$), proportion of males ($p = 0.708$), effect type ($p = 0.723$), whether confounding factors are adjusted ($p = 0.606$) might not be the source of heterogeneity. In addition, sickle cell trait (SCT) was significantly associated with the mortality (pooled ES = 1.54, 95% CI: 1.28–1.85, $p = 0.771$) and hospitalization (pooled ES = 1.20, 95% CI: 1.07–1.35 , $p = 0.519$) in patients with COVID-19. But any increased risk of ICU admission/severe (pooled ES = 1.24, 95% CI: 0.95–1.62, $p = 0.520$) and mechanical ventilation (OR = 1.00, 95%CI:0.59-1.69) in COVID-19 patients with SCT was not observed. Sensitivity analysis demonstrated that the results were robust. The results of the funnel plot and Egger's test did not support the existence of publication bias. Current meta-analysis indicated that sickle cell disorder has a meaningful impact on COVID-19 progression to severe cases and associated deaths. However, further investigations and research to validate the current findings is indispensable.

**Abbreviations:** 2019-nCoV, 2019 novel coronavirus; ACS, acute coronary syndrome; BET, blood exchange transfusion; BMI, body mass index; CI, confidence intervals; COVID-19, coronavirus disease 2019; ES, effect sizes; HbF, fetal hemoglobin; HbS, hemoglobin S; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCD, sickle cell disease; SCT, sickle cell trait.

  

KEYWORDS
adverse prognosis, COVID-19, meta-analysis, sickle cell disease, sickle cell trait

## 1 | INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] COVID-19 is spreading rapidly worldwide due to the viral pathogen causing the disease is severely infectious and can be transmitted from human to human.[2] People with COVID-19 have a wide and largely unpredictable clinical presentations that could range from mild asymptomatic infection to serious cases requiring an intensive care unit (ICU) bed admission or even death.[3] Evidence has shown that the presence of common diseases, including cardiovascular disease, hypertension, diabetes, high body mass index and cancers has a meaningful impact on severe COVID-19 disease and associated deaths.[4–8] Therefore, it is essential to identify high-risk groups of developing serious disease to reduce mortality and improve clinical outcomes in those patients.

Sickle cell disease (SCD) is an inherited disorder of hemoglobin molecular dysfunction caused by the homozygous inheritance of the mutant β-globin chain gene, while sickle cell trait (SCT) is caused by the heterozygous inheritance.[9,10] Individuals with SCD have immunodeficiency, chronic anemia, inflammatory responses, hypercoagulable status, organ damage and related comorbidities such as acute coronary syndrome (ACS) and occlusive thrombosis episodes that all could increase susceptibility to adverse COVID-19 outcomes.[10,11] Although generally considered benign carrier state and largely asymptomatic, SCT is associated with an elevated chance of unfavorable outcomes, including uncommon complications of exercise-related injuries,[12] renal medullary carcinoma[13] and common clinical conditions such as pulmonary embolism, renal disease.[14,15]

The worldwide pandemic of the novel coronavirus has raised concerns in the SCD population. Patients with sickle cell disorder were concerned about whether the combination of COVID-19 would lead to death or worse forms and complications of the disease. Although multiple prognostic factors that negatively affect COVID-19 disease outcomes have been demonstrated, it is unclear whether individuals with SCD/SCT have a greater probability of developing serious COVID-19 compared to those without sickle cell disorder. Therefore, the goal of this paper was to elucidate the relationship between sickle cell disorder and severe COVID-19 by pooling effect values.

## 2 | METHODS

### 2.1 | Literature search strategy

The objective of this study is to investigate the association between SCD and SCT with disease severity and risk of death in COVID-19 patients. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist was used to improve the reporting of this meta-analysis. We systematically retrieved all related papers in PubMed, Web of Science and Embase until August 20, 2023. To retrieve as complete a set of potential studies as possible, we used Pubmed (MeSH) and Embase (Emtree) to identify medical subject heading and all synonyms for SCD and combined them using OR. The same process was done for SCT and COVID-19. Finally, the full strings of SCD and sickle cell characteristics were merged using OR, and then the results were merged with the full strings of COVID-19 using AND. The medical subject heading, synonyms and exact search strings in the three literature databases Pubmed, Web of science, and Embase are presented in Supporting Information: Files Table S1 and Table S2. Furthermore, references that were available articles and important review articles need to be searched manually for other potentially eligible studies. After the search was completed, all candidate articles were further screened using inclusion and exclusion terms.

### 2.2 | Inclusion and exclusion criteria

The case group was considered to be COVID-19 patients with combined SCD/SCT, and the control group was considered to be COVID-19 individuals without SCD/SCT. The target outcomes we focused on were hospitalization, ICU admission/severe, respiratory failure/mechanical ventilation, and mortality. Studies with the following conditions were selected in our meta-analysis: (1) Studies should be published in English; (2) Articles that reported effect sizes (ES) and 95% confidence intervals (CI) between SCD/SCT and COVID-19 severity or studies that reported the number of outcomes according to the category with or without sickle cell disorders. No restriction was placed on the region of study. If studies were based on the same data sources, only the articles containing the most sufficient data were included. An article matching one of the following conditions was excluded: (1) Articles not published in English; (2) repeated articles; (3) meta-analysis, case reports, reviews, news, comment, guideline and expert consensus; (4) articles without sufficient information; (5) animal-based research, studies only on pregnant women.

### 2.3 | Data extraction

Two researchers independently screened all potentially relevant literature. The basic information listed below was extracted from all eligible articles: first author's name, geographic region, sample size, study design, age, the percent of males, disease type, percentage of SCD/SCT, outcomes of COVID-19 disease, effect estimates (including odds ratio [OR], risk ratio [RR], and hazard ratio [HR]) with 95% CI

and adjusted risk factors. In case of an objection arises during the extraction of the date, the relevant disputes are resolved through negotiation by a third person.

### 2.4 | Statistical analysis

We evaluated the relationship between SCD/SCT and severe COVID-19 based on the combined effect values with its corresponding 95% CIs. Study heterogeneity was evaluated by using both Chi-square tests with $p$ Values and $I^2$ statistics. The analysis is carried out using a fixed effects model when $I^2 \leq 50\%$ and, conversely, a random effects model. Sensitivity analysis was a reanalysis of the original or meta-analysis by excluding each study individually to detect the robustness of the combined results. If the pooled estimates did not change substantially after moving any one study and reanalyzing, this means that our results were robust. Publication bias was examined by using funnel plot and Egger's test. Meta-regression and subgroup analyses were used in ≥10 studies of the association between SCD or SCT and COVID-19 adverse outcomes to explore sources of heterogeneity. All statistical analyses in this meta-analysis were done by applying STATA software version 15.0.

## 3 | RESULTS

### 3.1 | Characteristics of selected studies

Database searches of PubMed, Web of Science and Embase yielded 295, 471, and 829 studies, respectively. In addition, an eligible study was available on Medrxiv by manual retrieval. Of these, 625 were excluded for duplicate studies. After reading the title and abstracts, 862 were excluded. One hundred and nine articles potentially eligible were assessed by reviewing the full texts. After discarding the meta-analysis, case reports, reviews, comments, articles with insufficient data or not published in English, and only on pregnant women, a total of 21 studies[14,16–35] satisfied the inclusion conditions and were selected in our meta-analysis. We drafted a flow chart that is fully consistent with the PRISMA guidelines (Figure 1). Of 21 included studies, four studies from Europe (from England), 13 from North America (from

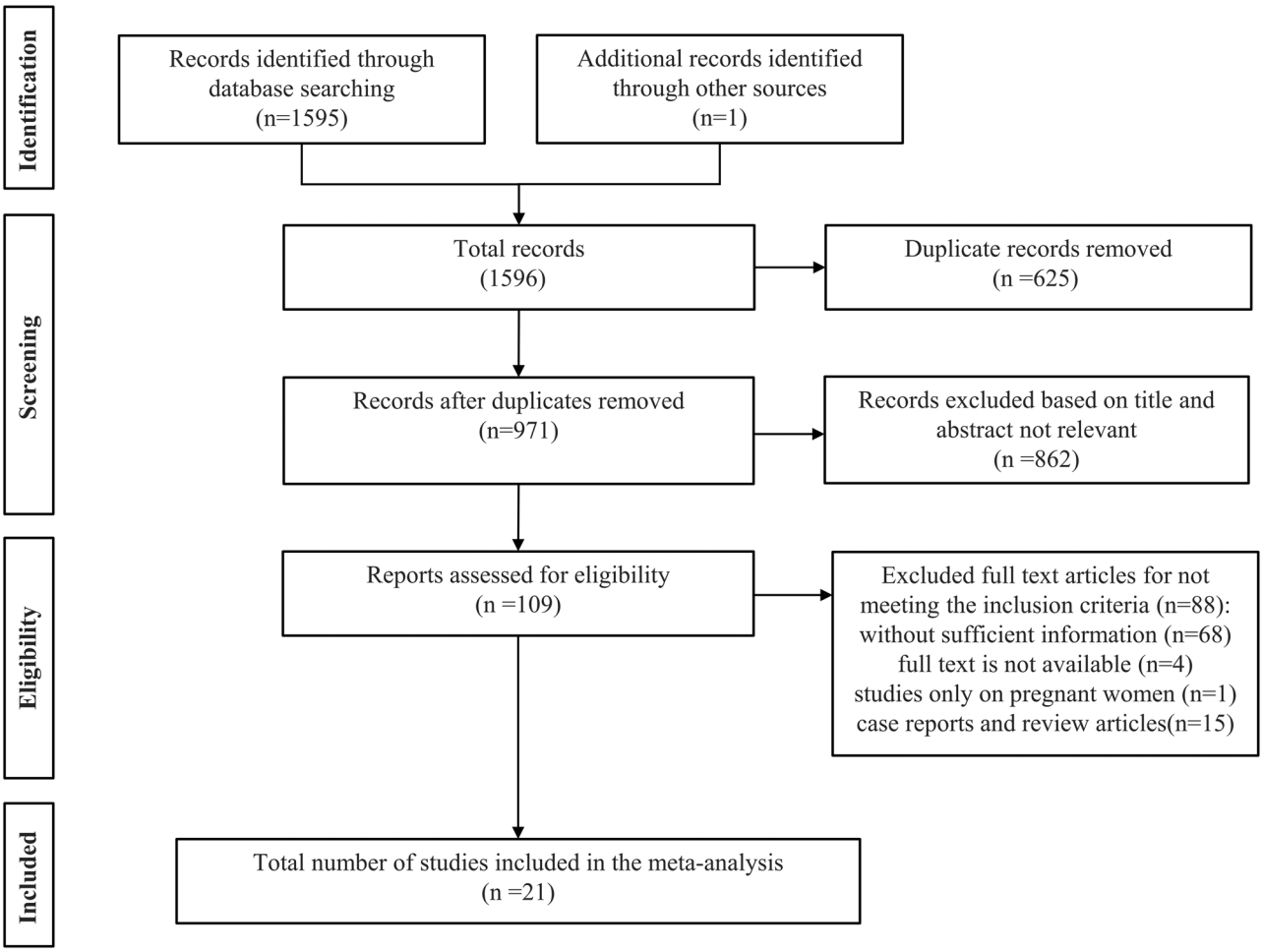


**FIGURE 1** Selection process for studies included in this meta-analysis. Twenty-one studies were included in the meta-analysis.

**TABLE 1** The main characteristics of the studies included.

| Author | Country | Study design | Sample size | Age(year) | Male (%) | Disease type | *n* (%) | Outcome | Effect estimates (95% CI) | Adjusted | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Boğa et al. | Turkey | A retrospective, multicenter, and cross-sectional study | 160 | Case: Mean age (range): 35 (18–64)<br>Control: Mean age (range): 35 (21–53) | 67 (41.9) | SCD | 39 (24.4) | Hospitalization | OR: 4.29 (1.6–11.54) | NA | |
| Hoogenboom et al. | American | Retrospective observational cohort study | 12 597 | Case: Median age (IQR): 30 (20–47)<br>Control: Median age (IQR): 57 (39–70) | 6047 (48.0) | SCD | 53 (0.4) | Hospitalization | OR: 7.26 (3.75–14.08) | adjusted for age, gender, race, ethnicity and comorbidity burden | 7 |
| | | | | | | | | ICU | OR: 1.07 (0.38–3) | | |
| | | | | | | | | Death | OR: 1.48 (0.42–5.15) | | |
| | | | | | | | | Mechanical ventilation | OR: 1.28 (0.39–4.19) | | |
| Hoogenboom et al. | American | Retrospective observational cohort study | 12 606 | Case: Median age (IQR): 47 (32–62)<br>Control: Median age (IQR): 57 (39–70) | 6032 (47.9) | SCT | 62 (0.5) | Hospitalization | OR: 1.07 (0.8–1.43) | adjusted for age, gender, race, ethnicity and comorbidity burden | 7 |
| | | | | | | | | ICU | OR: 1.11 (0.72–1.71) | | |
| | | | | | | | | Death | OR: 1.17 (0.75–1.83) | | |
| | | | | | | | | Mechanical ventilation | OR: 1.00 (0.59–1.69) | | |
| Clift et al. | England | Retrospective cohort study | 12 252 504 | Range: 0–100 | 6 137 011 (50.1) | SCD | 5059 (0.04) | Hospitalization | HR: 4.11 (2.98–5.66) | adjusted for age, sex, and ethnicity | 9 |
| | | | | | | | | Death | HR: 2.55 (1.36–4.75) | | |
| Clift et al. | England | Retrospective cohort study | 12 273 127 | Range: 0–100 | 6 144 570 (49.8) | SCT | 25 682 (0.21) | Hospitalization | HR: 1.38 (1.12–1.70) | adjusted for age, sex, and ethnicity | 9 |
| | | | | | | | | Death | HR: 1.51 (1.13–2.00) | | |

**TABLE 1** (Continued)

| Author | Country | Study design | Sample size | Age(year) | Male (%) | Disease type | *n* (%) | Outcome | Effect estimates (95% CI) | Adjusted | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ward et al. | England | Retrospective cohort study | 2891 | Range: 0–17 | NA | SCD | NA | ICU | OR: 1.07 (0.25–4.48) | adjusted for age, sex, IMD category and ethnicity | 7 |
| Campbell et al. | American | A multicenter retrospective cohort study | 1877 | Mean age: 15.3 ± 1.4 | 992 (53) | SCD | 27 (1.4) | Hospitalization | OR: 6.9 (3–15.9) | adjusted for race , ethnicity | 8 |
| Alhumaid et al. | Saudi Arabia | Retrospective cohort study | 1014 | Mean age: 47.2 ± 19.3 | 582 (57.4) | SCD | 31 (3.0) | ICU | OR: 3.41 (1.65-7.05) | NA | 6 |
| Castonguay et al. | Canada | Retrospective cohort study | 74 | Median age (IQR): 23(8 months-68) | 33 (44.6) | SCD | 74 (NA) | Hospitalization | OR: 15.7 (9.7–25.4) | NA | 5 |
| | | | | | | | | ICU | OR: 1 (0.4–2.5) | | |
| Adamkiewicz et al. | American | Retrospective | 2566 | Mean age: 50.1 ± 19.5 | NA | SCD | 48 (1.87) | Hospitalization | OR: 1.4 (1–2) | adjusted for age, gender and obesity | 7 |
| | | | | | | | | ICU | OR: 2.4 (1–5.8) | | |
| | | | | | | | | Death | OR: 2.2 (0.4–12.3) | | |
| | | | | | | | | Respiratory failure | OR: 2.1 (1.1–3.9) | | |
| Abdulrahman et al. | Bahrain | Retrospective cohort study | 1792 | Mean age: 46 ± 17 | 1057 (60.0) | SCD | 38 (0.17) | Death | OR: 0.80 (0.11–5.9) | NA | 7 |
| Dun et al. | American | Retrospective | 534 023 | Median age (IQR): 77 (70–85) | 226 428 (42.4) | SCD | 222 (0.04) | Death | OR: 1.73 (1.21–2.47) | adjusted for chronic kidney disease, prostate cancer, race, pressure ulcers and chronic ulcers, acute myocardial infarction, gender, and heart failure | 7 |
| Singh et al. | American | Retrospective cohort study | 45 829 | Case: Mean age ±SD: 45.0 ± 19.7<br>Control: Mean age ±SD: 31.4 ± 16.8 | 18 671 (40.8) | SCD | 312 (0.68) | Hospitalization | RR: 2 (1.5–2.7) | NA | 8 |
| | | | | | | | | Death | RR: 1 (0.4–2.4) | | |

(Continues)

**TABLE 1** (Continued)

| Author | Country | Study design | Sample size | Age(year) | Male (%) | Disease type | *n* (%) | Outcome | Effect estimates (95% CI) | Adjusted | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Respiratory failure/ mechanical ventilation | RR: 1.3 (0.8–2.0) | | |
| Dubois et al. | American | A multicenter retrospective cohort | 1574 | Mean age: 15.3 ± 1.4 | 739 (47.0) | SCD | 18 (1.1) | Hospitalization | OR: 3.4 (1.1–10.6) | adjusted for race and ethnicity | 6 |
| Resurreccion et al. | England | A population-based study | 7849 | Range: 40–69 | NA | SCT | 21 (0.27) | Death | OR: 2.87 (0.69–9.95) | adjusted for age at COVID-19 test, sex, and race | 8 |
| Verma et al. | African | Retrospective | 3749 | NA | NA | SCT | 323 (8.62) | Death | OR: 1.77 (1.13–2.77) | adjusted by sex, age | 7 |
| | | | | | | | | Hospitalization | OR: 1.17 (0.91–1.5) | | |
| | | | | | | | | Severe | OR: 1.33 (0.95–1.88) | | |
| Iyengar et al. | American | Retrospective | 13 841 | NA | NA | SCT | NA | Death | OR: 1.8 (1.14–2.84) | adjusted for sex, age, ethnicity, age2, and 20 genetic principal components | 7 |
| Merz et al. | American | A multicenter, retrospective study | 166 | Case: Median (range): 66 (22–81) Control: Median (range): 64 (22–103) | 86 (51.8) | SCT | 20 (12.04) | Death | OR: 1.18 (0.32–4.41) | NA | 7 |
| Castonguay et al. | Canada | A multicentric web-based retrospective study | 455 630 | Range: 0–69 | NA | SCD | 103 (0.06) | Hospitalization | OR: 5.15 (3.38–7.85) | NA | 8 |
| | | | | | | | | ICU | OR: 4.83 (2.11–11.01) | | |
| Ilerhunmwuwa et al. | American | Retrospective | 1 060 420 | Case: Median age (IQR): 42 (31) Control: Median age (IQR): 66 (23) | 560 005 (52.8) | SCD | 2870 (0.3) | Mechanical ventilation | OR: 0.74 (0.50–1.09) | Adjusted OR | 8 |
| | | | | | | | | Death | OR: 0.74 (0.48–1.15) | | |

**TABLE 1** (Continued)

| Author | Country | Study design | Sample size | Age(year) | Male (%) | Disease type | *n* (%) | Outcome | Effect estimates (95% CI) | Adjusted | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Paulukonis et al. | Georgia, American | state-level population-based retrospective cohorts | 68 097 | Range: 0–12 | 34 355 (50.5) | SCD | 147(0.22) | Hospitalization | OR: 20.2 (13.6–30.0) | Adjusted for sex and age | 9 |
| Paulukonis et al. | Georgia, American | state-level population-based retrospective cohorts | 70 247 | Range: 0–12 | 35 462 (50.5) | SCT | 2297(3.3) | Hospitalization | OR: 1 (0.7–1.5) | Adjusted for sex and age | 9 |
| Paulukonis et al. | Michigan, American | state-level population-based retrospective cohorts | 322 155 | Range: 0–33 | 159 315 (49.5) | SCD | 240 (0.07) | Hospitalization | OR: 14.8 (10.4–21.1) | Adjusted for sex and age | 9 |
| | | | | | | | | Death | OR: 11.2 (3.4-37.3) | | |
| Paulukonis et al. | Michigan, American | state-level population-based retrospective cohorts | 326 044 | Range: 0–33 | 161 138 (49.4) | SCT | 4129 (1.27) | Hospitalization | OR: 1.2 (0.9–1.5) | Adjusted for sex and age | 9 |
| | | | | | | | | Death | OR: 1.6 (0.7–3.8) | | |
| Ungar et al. | American | Retrospective | 4097 | Range: 0–20 | 2302 (56.2) | SCD | 38 (0.9) | Hospitalization | OR: 6.28 (3.06-12.87) | Adjusted for demographic factors | 7 |
| | | | | | | | | ICU | OR: 2.66 (0.94–7.49) | | |
| Shi et al. | England | A national incident cohort study | 752 868 | Range: 5–17 | NA | SCD | 400 (0.05) | Hospitalization | HR: 14.35 (8.48–24.28) | Adjusted for age, sex, socioeconomic status, other risk groups of interest, and prior hospitalization | 9 |

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; ICU, intensive care unit; IMD, index of multiple deprivation; IQR, interquartile range; NA, not available; OR, odds ratio; RR, risk ratio; SCD, sickle cell disease; SCT, sickle cell trait.

America and Canada), three from Asia (from Turkey, Saudi Arabia, and Bahrain, respectively), and the last one from Africa. Fourteen studies reported effect values between SCD and COVID-19 hospitalization, seven articles reported SCD and ICU admission/severe, eight articles reported SCD and mortality and four articles reported SCD and respiratory failure/mechanical ventilation. In addition, five studies reported effect values between SCT and COVID-19 hospitalization, two articles reported ICU admission, seven articles reported mortality and one article reported respiratory failure/mechanical ventilation. Of the 21 articles, only one was a cross-sectional study[16] and the rest were cohort studies. The Newcastle-Ottawa Scale (NOS) is the most commonly used tool today for assessing the methodological quality (risk of bias) of cohort studies.[36] Therefore, the NOS scale was used to score the quality of the included literature. High-quality studies referred to studies with scores greater than or equal to 6. The key characteristics of eligible studies were detailed in the Table 1 in detail.

## 3.2 | Relation between SCD and COVID-19 adverse outcomes

Overall, our findings showed a statistically significant relationship between SCD and an increased probability of mortality (pooled ES = 1.70, 95%CI: 1.00–2.92, $I^2 = 72.6\%$, $p = 0.001$, random-effects model) (Figure 2A), hospitalization (pooled ES = 6.21, 95% CI: 3.60–10.70, $I^2 = 94.4\%$ , $p = 0.000$ , random-effects model) (Figure 2B) AND ICU admission (pooled ES = 2.29, 95% CI: 1.61–3.24, $I^2 = 43.8\%$ , $p = 0.099$, fixed-effects model) (Figure 2C) for COVID-19 compared to those without SCD based on 8, 13, and 7 eligible studies reporting effect estimates, respectively. Patients with SCD had an increased risk of respiratory failure/mechanical ventilation, but a statistical association was not found (pooled ES = 1.21, 95%CI: 0.74–1.98, $I^2 = 64.9\%$, $p = 0.036$, random-effects model) (Figure 2D). There was significant heterogeneity between SCD and death, hospitalization, and respiratory failure/mechanical ventilation. Only SCD and hospitalization included ≥10 studies, so meta-regression and subgroup analysis were used to explore

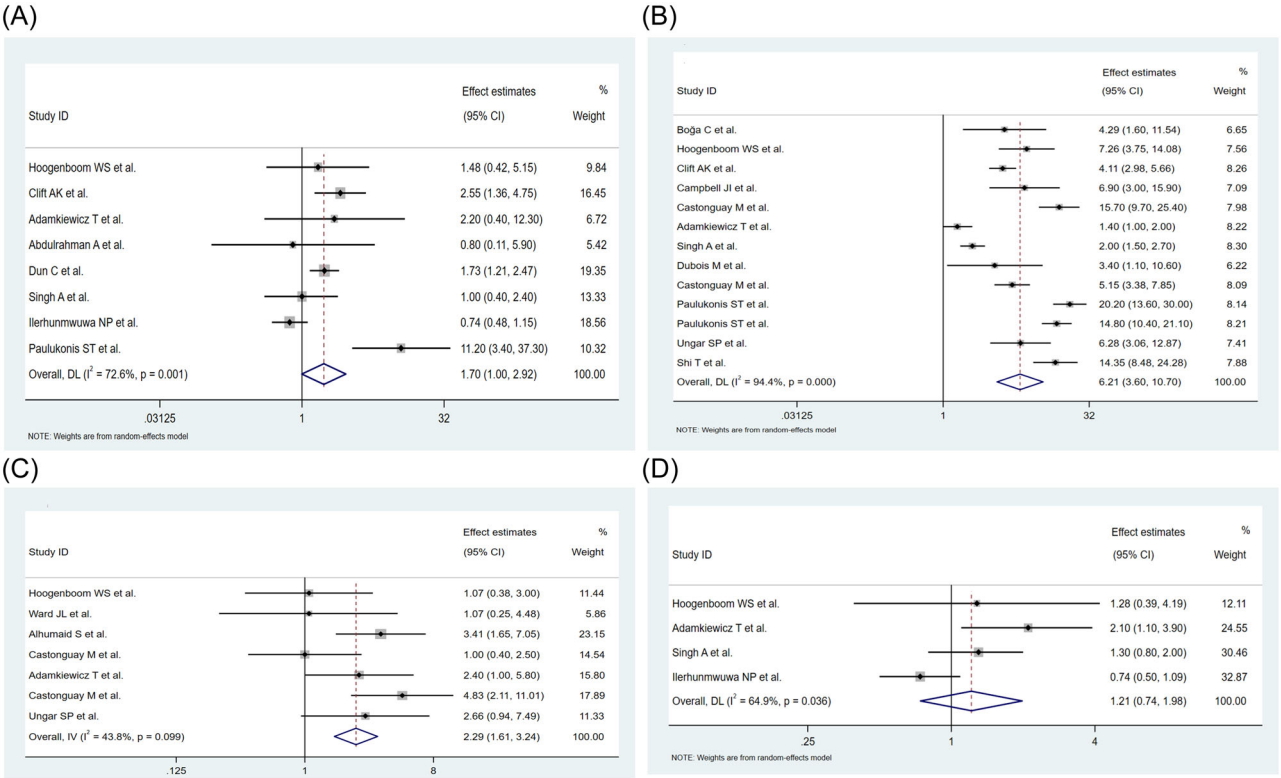


**FIGURE 2** Forest plots of the meta-analysis of the association of SCD with adverse outcomes of COVID-19. A random-effects model was used for meta-analysis to summarize the combined effect values and the corresponding 95% CI. (A) Forest plot of the meta-analysis of SCD associated with mortality. Significant heterogeneity was observed among studies ($I^2 = 72.6\%$, $p = 0.001$); (B) Forest plot of meta-analysis of SCD associated with hospitalization. Significant heterogeneity was observed among studies ($I^2 = 94.4\%$, $p = 0.000$); (C) Forest plot of meta-analysis of SCD associated with ICU admission. There was no significant heterogeneity ($I^2 = 43.8\%$, $p = 0.099$); (D) Forest plot of meta-analysis of SCD associated with respiratory failure/mechanical ventilation. There was significant heterogeneity in these studies ($I^2 = 64.9\%$, $p = 0.036$). CI, confidence interval; ICU, intensive care unit; SCD, sickle cell disease.

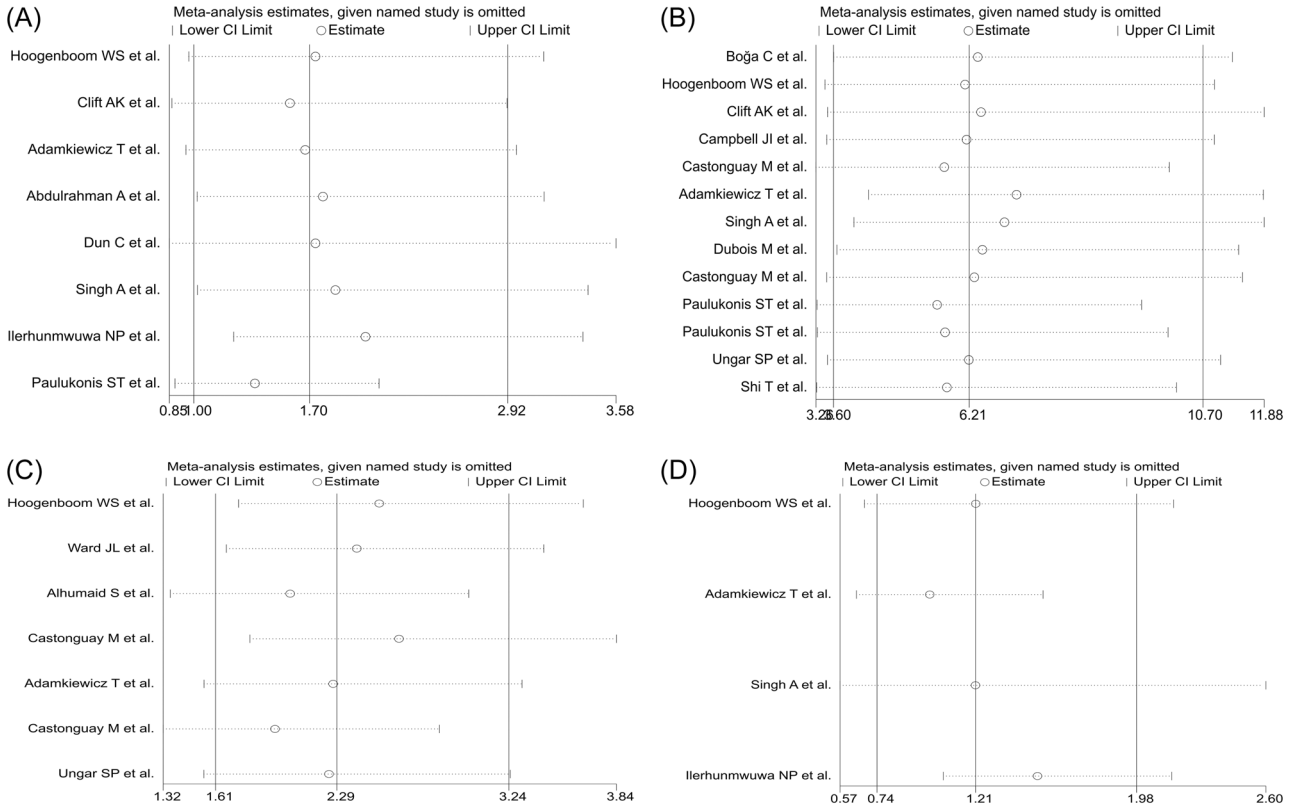


**FIGURE 3** Sensitivity analysis of the adverse outcomes of SCD for COVID-19. Sensitivity analysis was a reanalysis of the original or meta-analysis by excluding each study individually to detect the robustness of the combined results. (A) mortality; (B) hospitalization; (C) ICU admission; (D) respiratory failure/mechanical ventilation. Sensitivity analysis showed stable results for meta-analysis of SCD and COVID-19 hospitalizations, ICU admission and respiratory failure/mechanical ventilation. ICU, intensive care unit; SCD, sickle cell disease.

the source of heterogeneity. Meta-regression suggested that the tested variables including Area ($p = 0.642$), study design ($p = 0.739$), sample size ($p = 0.397$), proportion of males ($p = 0.708$), effect type ($p = 0.723$), whether confounding factors are adjusted ($p = 0.606$) might not be the source of heterogeneity. The results of subgroup analysis and meta-regression analysis of SCD and hospitalization were presented in the Supporting Information: File Table S3. Sensitivity analysis demonstrated that the results were robust (Figure 3). With regard to the possibility of publication bias, the results of the funnel plot (Figure 4) and Egger's test did not support the existence of publication bias, mortality ($p = 0.542$), hospitalization ($p = 0.404$), ICU ($p = 0.142$) and respiratory failure/mechanical ventilation ($p = 0.468$)

### 3.3 | Relation between SCT and COVID-19 adverse outcomes

Our results demonstrated a statistically significant relationship between SCT and an elevated likelihood of mortality (pooled ES = 1.54, 95%CI: 1.28–1.85, $I^2 = 0.0\%$, $p = 0.771$, fixed-effects model) (Figure 5A) and hospitalization (pooled ES = 1.20, 95% CI: 1.07–1.35, $I^2 = 0.0\%$, $p = 0.519$, fixed-effects model) (Figure 5B) for COVID-19 as well. But a risk of ICU admission/severe (pooled ES = 1.24, 95%CI: 0.95–1.62, $I^2 = 0.0\%$, $p = 0.520$, fixed-effects model) (Figure 5C) AND mechanical ventilation (OR = 1.00, 95%CI: 0.59–1.69) in COVID-19 patients with SCT was not observed. Sensitivity analysis of SCT and mortality showed that no substantial variation in pooled estimates, implying that the meta-analysis results were robust (Figure 6). The results of the funnel plot (Figure 7) and Egger's test did not support the existence of publication bias, mortality ($p = 0.629$), hospitalization ($p = 0.055$).

## 4 | DISCUSSION

Because COVID-19 is a serious threat to a patient's life, and its severe disease forms are mostly unpredictable, identifying risk factors related to COVID-19 outcomes has become a research priority. Our findings indicated that both SCD and SCT were contributing factors to the adverse consequences of COVID-19. The Centers for Disease Control and Prevention reported results consistent with this meta-analysis, which confirms our findings.[37,38] Understanding the possible mechanisms behind the negative impact of sickle cell disorder on COVID-19 individuals is crucial for the management of these patients as well as their prognosis. The pathologic physiology of sickle cell disorder is characterized by a chronic inflammatory process, with a greater incidence

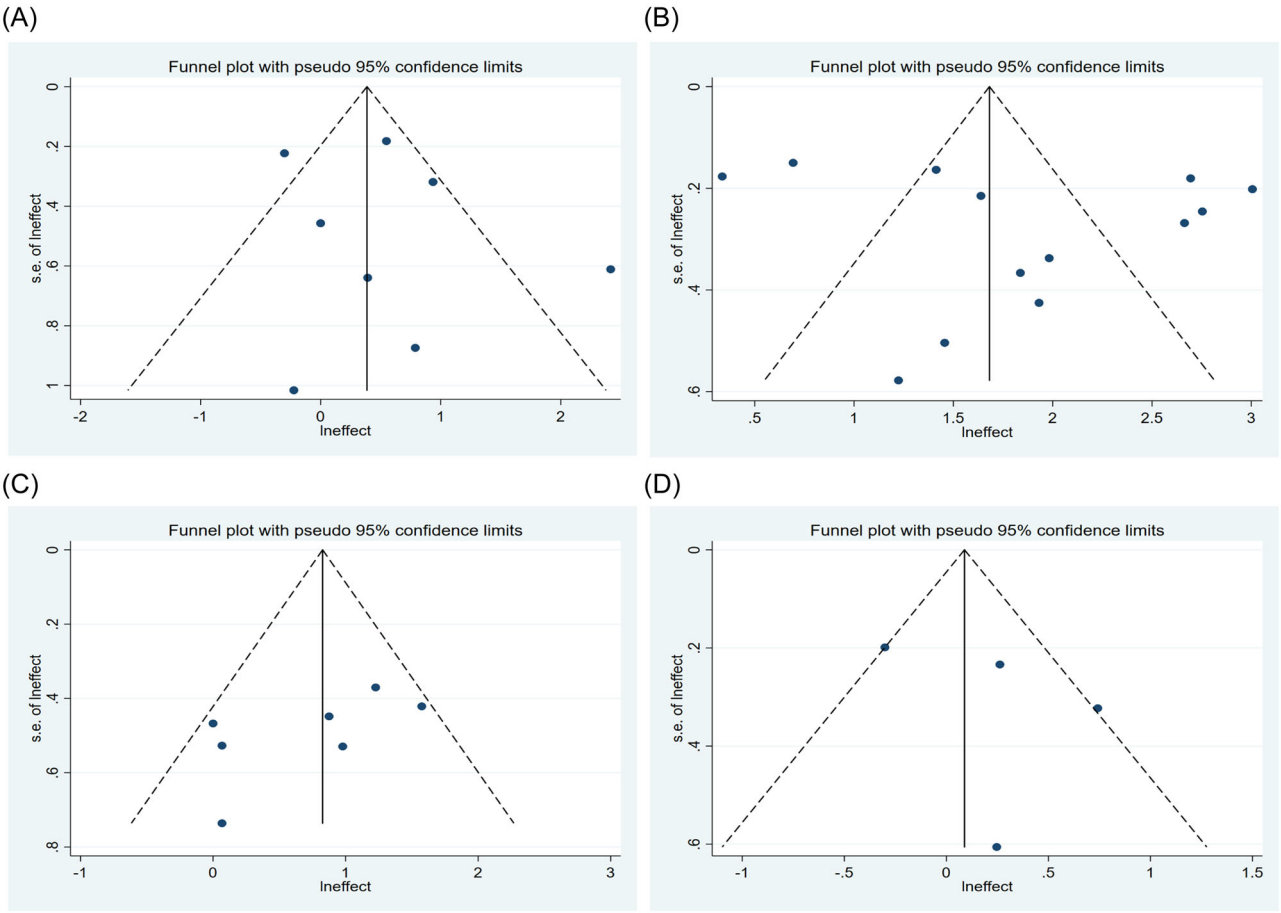


**FIGURE 4** Funnel plot of the adverse outcomes of SCD for COVID-19. Each circle represents a separate study. The horizontal axis refers to the ln effect estimates, and the vertical axis represents the standard error of the ln effect estimates. (A) mortality; (B) hospitalization; (C) ICU admission; (D) respiratory failure/mechanical ventilation. The results of the funnel plot and Egger's test did not support the existence of publication bias, mortality ($p = 0.542$), hospitalization ($p = 0.404$), ICU ($p = 0.142$) and respiratory failure/mechanical ventilation ($p = 0.468$). ICU, intensive care unit; SCD, sickle cell disease.

of thrombotic and vaso-occlusive events due to the potential proinflammatory response mechanism and thrombogenic state.[39,40] Vascular occlusion and hemolytic anemia can trigger a wide range of acute clinical events, including tissue ischemia and infarction, leading to severe pain or chronic end-organ damage.[9] In addition, SARS-CoV-2 infection can cause decreased oxygen saturation and subsequent peripheral blood hypoxia, which lays the foundation for the polymerization of hemoglobin S (HbS) into polymers in SCD patients. When the number of HbS polymers reaches a certain level, it causes the deformability of erythrocytes at the ends of arterioles to decrease and become sickle-shaped, thus promoting vaso-occlusive episodes and severe pain.[9,41] Viral infections can also be escalated by the pathophysiological changes specific to SCD, particularly influenza.[42] Sickle cell individuals are known to be susceptible to infections due to structural defects in their resistance to infections such as immune system dysfunction and reduced organ reserves.[16] Patients are particularly susceptible to infectious diseases such as sinopulmonary and recurrent urinary tract infections as well as ACS due to defective phagocytosis and immune deficiency as a result of their own splenic infarction or surgical splenectomy.[9] The ACS is a classic case of organ failure in SCD and may be a contributing factor to severe COVID- 19.[43] COVID-19 can also lead to serious pulmonary complications by triggering ACS, creating a vicious cycle.[44] In addition, patients with SCD develop neurological complications and cardiopulmonary complications such as cardiomyopathy,[45,46] all of which can expose them to more critical disease outcomes.[47]

Arlet JB et al. reported that in a multivariate analysis adjusted for confounders, the compound heterozygous genotypes SC of SCD and age were strong independent adverse prognostic factors for death or critical cases in people with COVID-19.[48] In the US, Panepinto et al. found a more than 2-fold higher risk of death among outpatients or in patients with the SC genotype compared to COVID-19 with the SS genotype.[49] It is evident that patients with the SC type have a particularly susceptibility to the severe consequences of COVID-19. This possible reason is that SC patients have higher hemoglobin levels and blood viscosity, lower hemolysis rates and fetal hemoglobin levels compared to SS genotype patients,[50] which partially explain the pathogenic mechanism of several complications in individuals with SC genotype, and this would be a new research direction.

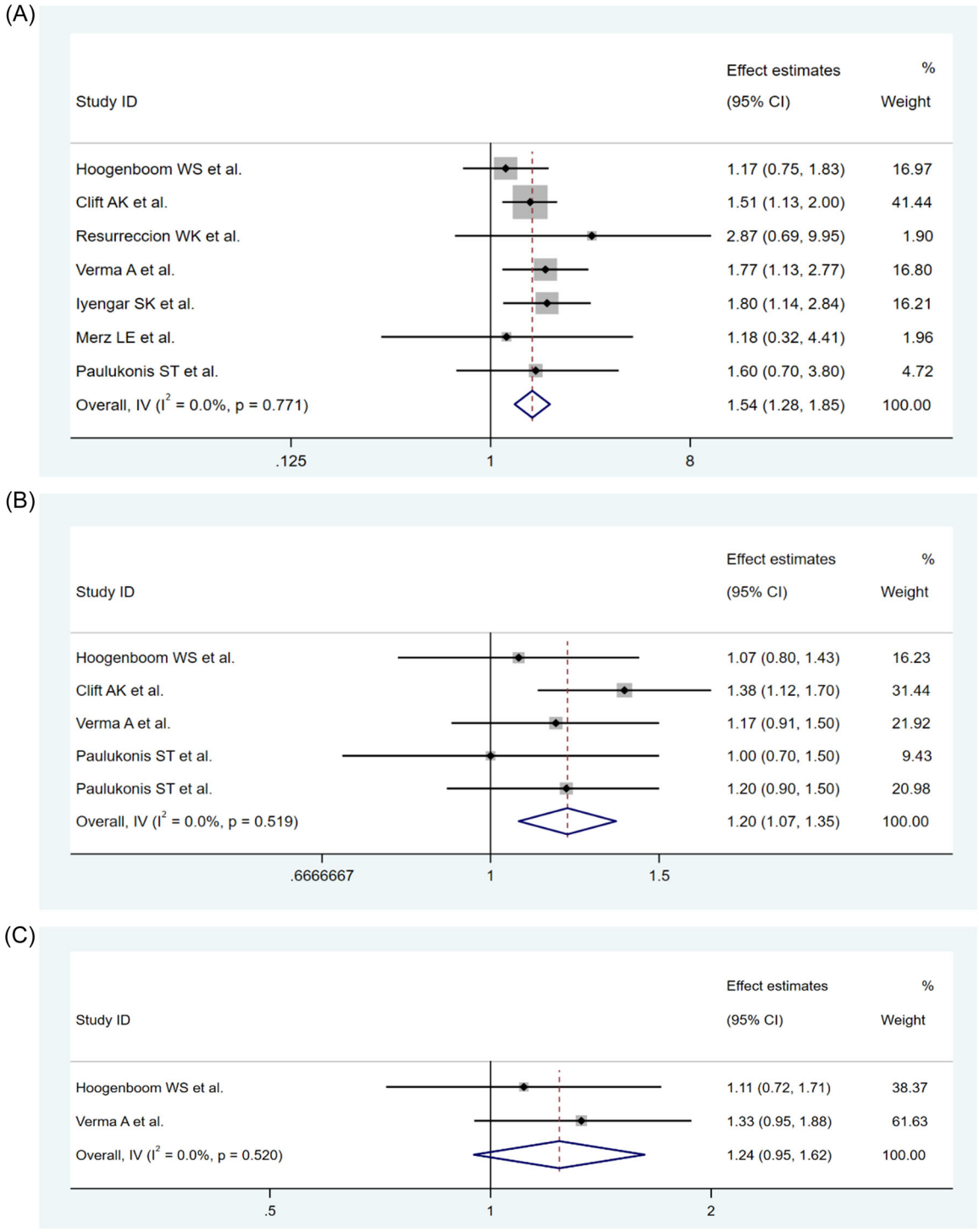


**FIGURE 5** Forest plots of the meta-analysis of the association of SCT with adverse outcomes of COVID-19. (A) Forest plot of the meta-analysis of SCT associated with mortality. There was no significant heterogeneity was observed among studies ($I^2 = 0.0\%$, $p = 0.771$); (B) Forest plot of the meta-analysis of SCT associated with hospitalization. There was no significant heterogeneity ($I^2 = 0.0\%$, $p = 0.519$); (C) Forest plot of the meta-analysis of SCT associated with ICU/severe. There was no significant heterogeneity ($I^2 = 0.0\%$, $p = 0.520$). SCT, sickle cell trait.

Therefore, if SC genotype and older were the majority of patients, the likelihood of severe case and death from COVID-19 would be greatly increased. Indeed, this particular vulnerability of the SC genotype does not appear to be limited to infection with the 2019 novel coronavirus. Both studies by Rankine-Mullings A et al. and Elenga N et al. found higher rates of severe dengue fever and mortality in the SC genotype than with the SS genotype.[51,52] Similar to SARS-CoV-2, the dengue virus also causes defective endothelial cell damage and repair function, as well as increased capillary endothelial cell permeability in response to the inflammatory

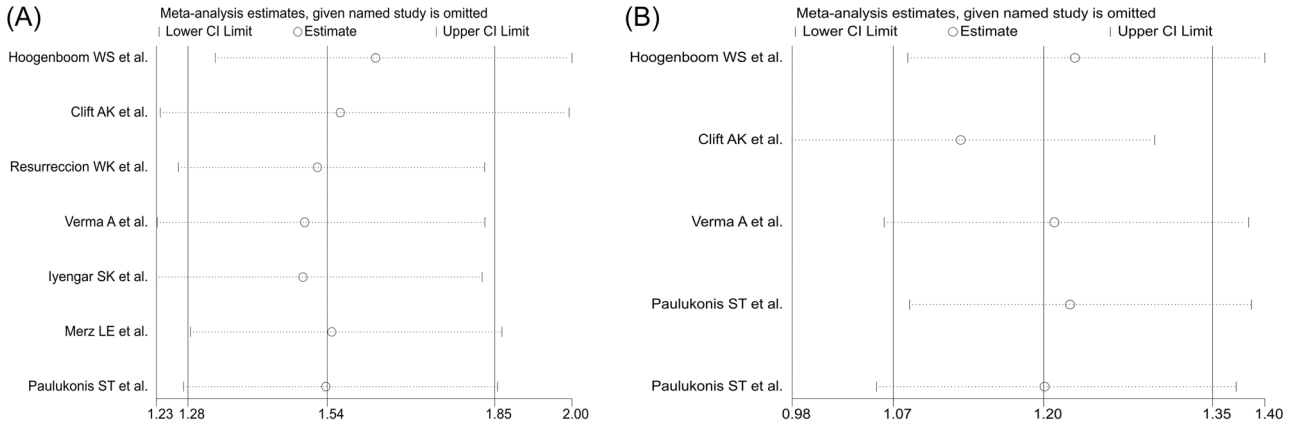


**FIGURE 6** Sensitivity analysis of the adverse outcomes of SCT for COVID-19. (A) mortality; (B) hospitalization. Sensitivity analysis showed stable results for meta-analysis. SCT, sickle cell trait.

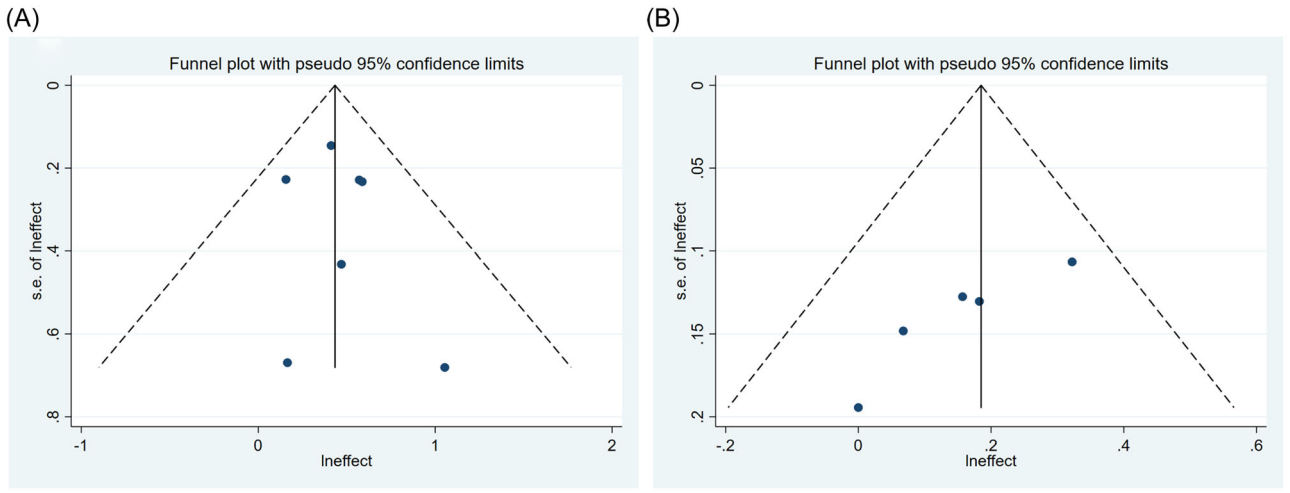


**FIGURE 7** Funnel plot of the adverse outcomes of SCT for COVID-19. (A) mortality; (B) hospitalization. The results of the funnel plot and Egger's test did not support the existence of publication bias, mortality ($p = 0.629$), hospitalization ($p = 0.055$). SCT, sickle cell trait.

response, leading to massive vascular leak syndrome and shock.[51,53] This raises issues on SC genotype patients promoting endothelial cell dysfunction leading to a specific vulnerability to viruses.

Therefore, in practical clinical treatment, doctors should give more attention to COVID-19 individuals with SCD, focus on the possible bidirectional relationship between sickle cell disorder and 2019-nCoV disease, and apply drugs in a timely manner to prevent worse outcomes. There is objective evidence that hydroxyurea reduces the rate of hemolysis and intracellular aggregation of HbS,[54] so it is recommended that hydroxyurea be initiated or maintained in all eligible patients with SCD, which will bring about an improvement in the patient's condition. Close medical surveillance and additional precautions for individuals with SC genotype and a history of ACS to prevent patients from progressing to the severe stage and thus increasing the disease burden on society. Early blood exchange transfusion (BET) and tocilizumab are strongly recommended when a sickle cell patient with COVID-19 has already developed complications of ACS and/or pulmonary embolism, regardless of hemoglobin genotype.[55] In addition, clinically, regardless of whether COVID-19 patients exhibit corresponding clinical signs and symptoms, SARS-COV-2 RT-PCR should be performed promptly when SCD patients present with suspected ACS symptoms.

However, several limitations should be acknowledged. First, we only included articles published in English, which may have led to the exclusion of studies in other suitable languages, potentially leading to publication bias. In addition, retrospective studies accounted for the majority of selected studies, so more prospective studies are needed to validate our results. Lastly, the meta-analysis included unadjusted crude effect values, thus the presence of some confounding factors that might affect the results, such as age, gender, or ethnicity, could not be excluded.

In conclusion, our findings indicate that sickle cell disorder has a meaningful impact on COVID-19 progression to severe cases and associated deaths. Timely diagnosis, early treatment, special clinical care techniques and management protocols together with current COVID-19 vaccine immunization are therefore essential to reduce the morbidity and mortality of these patients. This study provided strong objective evidence to clarify the relationship between sickle cell disorder and the severe

consequences of COVID-19. Moreover, further investigations and research to confirm the current findings are indispensable.

## AUTHOR CONTRIBUTIONS

Tianyi Liang and Kaixin Guo contributed to determining the outline and content of the meta-analysis. Tianyi Liang, Kaixin Guo, Peng Ni, Guangcai Duan, and Rongguang Zhang contributed to retrieving literature. Tianyi Liang contributed to the data analysis and the drafting of this manuscript. All authors contributed to revising the draft critically for important intellectual content, providing final confirmation of the revised version, and being responsible for all aspects of the work. The authors read and approved the final manuscript.

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## CONFLICT OF INTEREST STATEMENT

The author declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

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

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