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Liver and renal biochemical profiles of people with sickle cell disease in Africa: a systematic review and meta-analysis of case-control studies

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Abstract

Background Sickle cell disease (SCD) is a genetic blood disorder characterized by a painful vaso-occlusive crisis due to the sickling of red blood cells in capillaries. Complications often lead to liver and renal dysfunctions, contributing to morbidity and mortality, particularly for children under 5. This systematic review and meta-analysis aimed to evaluate the liver and renal functions of people with SCD (HbSS) compared to those without it (HbAA) in Africa.

Methods The protocol was registered with PROSPERO (CRD42022346771). We searched PubMed, Embase, Web of Science, and Google Scholar using the keywords "liver function", "renal function", "sickle cell disease", and "Africa" on 6th May 2023 for peer-reviewed articles with abstracts in English. We included case-control studies comparing SCD (HbSS) with controls without hemoglobinopathies (HbAA). We used the random-effect model to calculate the pooled average values for the blood tests of people with SCD in RStudio version 4.2.2.

Results Overall, 17 articles were analyzed from five African countries involving 1312 people with SCD and 1558 controls. The pooled mean difference of liver enzymes aspartate transaminase (AST) was 8.62 (95% CI − 2.99–20.23, $I^2 = 97.0\%$, $p < 0.01$), alanine transaminase (ALT) 7.82 (95% CI − 0.16–15.80, $I^2 = 99\%$, $p < 0.01$) and alkaline phosphatase (ALP) − 2.54 (95% CI − 64.72 – 59.64, $I^2 = 99\%$, $p < 0.01$) compared to controls. The pooled mean difference for the renal biochemical profiles creatinine − 3.15 (95% CI − 15.02; 8.72, I^2=99%, $p < 0.01$) with a funnel plot asymmetry of $t = 1.09$, df = 9, $p = 0.3048$ and sample estimates bias of 6.0409. The pooled mean difference for serum urea was − 0.57 (95% CI − 3.49; 2.36, $I^2 = 99\%$, $p < 0.01$), and the estimated glomerular filtration (eGFR) rate was 19.79 (95% CI 10.89–28.68 mL/min/1.73 m^2, $I^2 = 87\%$, $p < 0.01$) compared to controls.

Conclusion People with SCD have slightly elevated liver enzymes and estimated glomerular filtration rates compared to controls in Africa. With all the heterogeneity (I^2) > 50%, there was substantial variation in the reported articles' results.

Systematic review registration PROSPERO CRD42022346771

Keywords Sickle cell, Liver function, Renal function, Systematic review, Africa

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Introduction

Sickle cell disease (SCD) is an autosomal recessive disease affecting normal β-globin function [1, 2]. It results from a point mutation in the short arm of chromosome 11, where the amino acid, glutamic acid, is replaced by valine at position 6 of the β-globin chain [1, 2]. That reduces the flexibility of the red blood cells under low oxygen tension in end organs, leading to the "sickling" of the red blood cells [1, 2]. Acute vaso-occlusive pain is caused by the entrapment of erythrocytes in the microcirculation, causing vascular obstruction and tissue ischemia [3]. Vaso-occlusion and ischemia of major organs may lead to life-threatening multi-organ failure [3–5]. Renal dysfunction may present as glomerular hyperfiltration and proteinuria [6–18], while liver dysfunction includes elevated liver enzymes, especially alanine transaminase (ALT) and aspartate transaminase (AST) [7, 11, 19–22].

SCD can cause progressive injury to the liver with significant fibrosis and decreased liver function by adulthood [5, 23]. The tissue ischemia experienced during vaso-occlusive crises also affects their major organs, explaining some SCD symptoms [3, 5]. Asymptomatic patients may have hepatomegaly and elevated liver enzyme levels [3, 5]. This is not affected by sex or gender [24]. Elevated liver enzymes may also signify viral hepatitis acquired from multiple transfusions [3, 5, 19, 23, 24]. However, most patients with SCD are given life-long treatment; therefore, drug toxicity-related liver injury cannot be excluded [25–27].

Hypoxia, acidosis, and hypertonicity resulting from multiple vaso-occlusive crises promote sickling, leading to endothelial injury and more vaso-occlusion [4]. The resultant renal medullary ischemia and infarction lead to a gradual loss of glomerular function [4]. The defective proximal tubular function may result in increased creatinine clearance due to increased creatinine secretion, therefore increasing the estimated glomerular filtration rate (eGFR) [4], especially in children [3, 4, 28]. This may also explain the reduced serum creatinine and normal urea levels in sickle cell disease [4]. Prolonged use of hydroxyurea was found to reduce glomerular hyperfiltration rate and protect against multi-organ damage in sickle cell patients [29, 30]. However, people with SCD are advised to stay hydrated always as part of their prophylaxis against vaso-occlusive crises. Their good hydration status may also result in good glomerular perfusion leading to hyperfiltration compared to controls [31]. Focal glomerular injury may progress to renal failure with age [4].

Approximately five percent of the world's population carries the genes for hemoglobin disorders, with SCD being the most common among them [32, 33]. The prevalence of sickle cell genes is higher in sub-Saharan Africa, with 20–30% in western and eastern Africa [32, 33]. It is a major cause of mortality for every age group [34–36].

The Western and Eastern African people are known to consume foods with antisickling activities [37, 38]. Perhaps these foods modify the course of SCD and enable a higher chance of survival beyond 5 years of age. In Nigeria, niprisan (made from pepper seeds, clove flower buds, caprium stem, sorghum leaves, and "trona") [38] and Cajanus cajan (pigeon peas) [37] are foods with antisickling properties commonly used to treat SCD [37, 38]. Therefore, this systematic review and meta-analysis evaluated the liver and renal function biochemical profiles of people with SCD in Africa.

Methods

Following registration in PROSPERO: CRD42022346771, we conducted this review according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for systematic reviews and meta-analysis [39] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline [40]. A review question generated using the Condition, Context, and Population (CoCoPop) guidelines by the Joanna Briggs Institute [41] was used. The condition was "liver function test" and "renal function test"; the context was "Africa," and the population was "individuals living with SCD." Therefore, the research question was, "What are the renal and liver biochemical profiles of people living with SCD (HbSS) compared to controls (HbAA) in Africa?" The following keywords were used to identify potential articles on 6th May 2023 from PubMed, Embase (OVID), Web of Science, and Google Scholar: "sickle cell", "liver function test", "renal function test", and "Africa". The search included papers from inception to 6th May 2023. The search strategy is presented in Supplementary file 1.

All identified articles were entered into Endnote for screening and removal of duplicates. The screen adhered to the following criteria: (i) observational studies reporting liver or renal function tests of people with SCD in Africa, (ii) in all languages (with abstracts in English), and (iii) peer-reviewed. Case reports, editorial, and qualitative studies were excluded. Two authors independently screened the title and abstract of each article, and in case of any discrepancies, the third author made the final decision by consensus. The same team followed the same procedure for full-text review, risk of bias, and data entry. All articles were assessed using the ROBINS-E, a tool for assessing the risk of bias in non-randomized studies of exposure [42]. The data extracted from each article included sample size, number of individuals with SCD tested for liver and renal function and their controls, study design, and study setting (country and city).

Statistical analysis

Data analysis was performed using RStudio version 4.2.2. Numerical continuous variables were summarized as mean and standard deviation. Heterogeneity across individual studies was assessed using Higgins's inconsistency Q statistics and reported as I^2 and p value. A random-effect model meta-analysis was performed for pooled outcomes with I^2 of $\geq$ 50%. The regression-based Egger test and visual evaluation of contour-enhanced funnel plots were assessed for small-study effects and risk of bias.

Results

One thousand thirty-three articles were identified. Of this, 1016 were excluded, and only seventeen were included in the final synthesis. A summary of the data extraction processes is outlined in Fig. 1.

Characteristics of excluded studies

We failed to retrieve the full-text article for two studies. The other excluded studies had no abstracts or full-text available, no results for controls, poster presentations, beta thalassemia studies, only sickle cell traits (HbAS) without HbSS or studies of HbSS without HbAA controls for comparison, as shown in the Supplementary file 2.

Characteristics of included studies

Most of the studies were conducted in Nigeria ($n = 08$). All the studies were observational studies with low sample sizes (ranging between 40 and 340). Liver and renal function tests are shown in Tables 1 and 2, respectively. Different authors used different units of measurement for the tests. For example, some authors used IU/L (international unit per liter of blood) [7, 19], µmol/L [20], and others used µkat/L (microunit per liter) [11] to measure liver enzymes. The final results reflected here were converted to most units used by other authors using an online tool at ScyMed® [43]. Details are found in Supplementary file 4. All liver enzyme units were converted to IU/L.

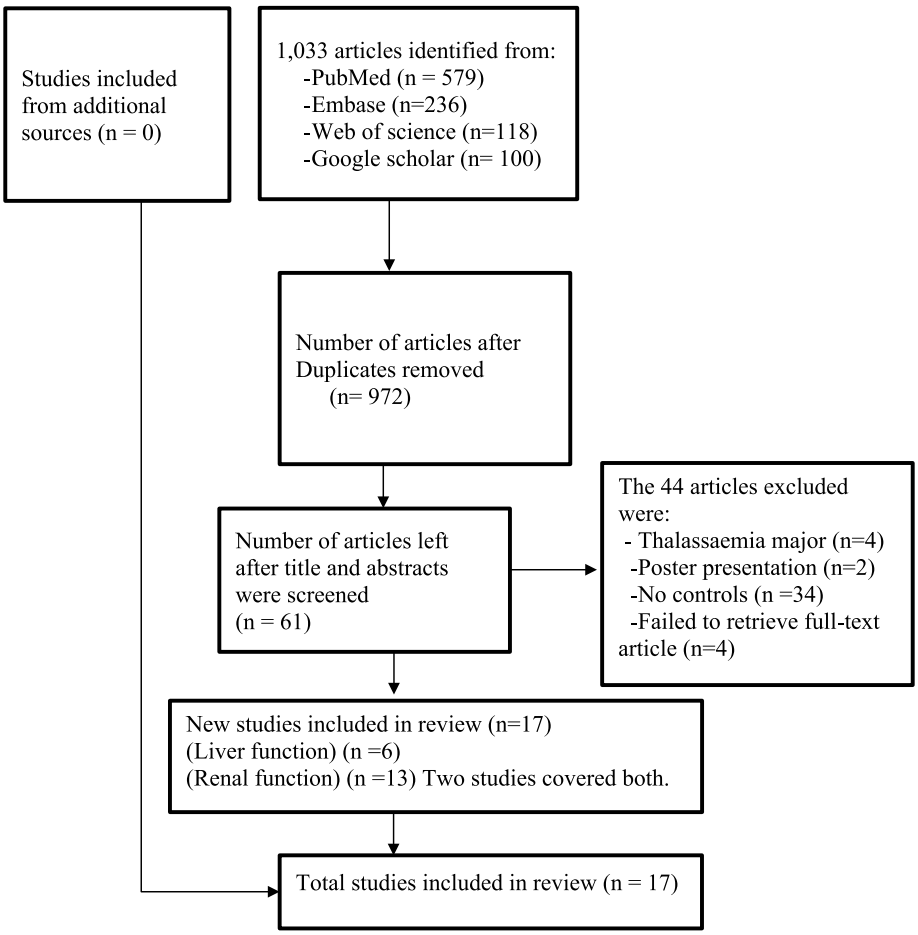

Fig. 1 Flow diagram for data selection. Adapted from The PRISMA 2020 statement: an updated guideline for reporting systematic reviews [40]

Table 1 Liver function tests of people with sickle cell disease in Africa

Authors	Setting	Study design	SCD/controls	Liver function
Asaolu et al. 2010	Ekiti, Nigeria	Prospective case-control study	42/42	ALP mean = 133.23, sd = 61.69; ALT mean = 28.68, sd = 9.85; AST mean = 20.42, sd = 10.94 [7]
Obi et al. 2020	Benin City, Nigeria	Prospective case-control study	50/50	ALT mean = 29.64, sd = 13.32; AST mean = 42.14, sd = 25.10 [21]
Mohamed et al. 1992	Khartoum, Sudan	Prospective case-control study	84/28	ALT mean = 93.37, sd = 37.95; AST mean = 37.70, sd = 21.50 [11]
Akuyam et al. 2017	Zaria, Nigeria	Prospective case-control study	100/100	ALP mean=108.8, sd = 5.40; ALT mean = 34.87, sd = 17.94; AST mean = 40.98, sd = 19.81 [19]
Saha 1982	Khartoum, Sudan	Prospective case-control study	5/320	ALT mean = 33.00, sd = 2.51; AST mean = 35.00, sd = 2.32 [20]
Yahaya 2012	Kano, Nigeria	Prospective case-control study	150/100	ALP mean = 82.67, sd = 10.87; ALT mean = 41.00, sd = 1.80; AST mean = 20.00, sd = 0.90 [22]

ALP alkaline phosphatase, *sd* standard deviation, *ALT* alanine transaminase, *AST* aspartate transaminase

Table 2 Renal function tests of people with sickle cell disease in Africa

Authors	Setting	Study design	Sample size SCD/controls	Renal function
Kambale-Kombi et al 2022	Kisangani, D R Congo	Prospective case-control study	98/89	creatinine mean = 52.59, sd = 18.59; urea mean = 5.05, sd = 1.82; eGFR mean = 119.90, sd = 53.78 [10]
Ndour et al. 2022	Dakar, Senegal	Prospective case-control study	163/177	creatinine mean = 52.17, sd = 20.34; urea mean = 7.00, sd = 4.50 [12]
Olawale et al. 2021	South-west, Nigeria	Prospective case-control study	150/50	creatinine mean = 47.75, sd = 0.88; urea mean = 16.80, sd = 1.30; eGFR mean = 122.50, sd = 9.00 [16]
Suliman et al. 2020	Khartoum, Sudan	Prospective case-control study	32/23	creatinine mean = 57.47, sd = 15.92; urea mean = 21.60, sd = 8.40; eGFR mean = 149.70, sd = 29.60 [17]
Nnaji et al. 2020	Owerri, Nigeria	Prospective case-control study	60/60	creatinine mean = 44.24, sd = 17.68; eGFR mean = 146.50, sd = 31.10 [13]
Farouk et al. 2020	Maiduguri, Nigeria	Prospective case-control study	110/110	eGFR mean = 125.90, sd = 31.90 [9]
Tantaway et al. 2017	Cairo, Egypt	Prospective case-control study	53/40	Creatinine mean = 43.33, sd = 8.84 [18]
Obalide et al. 2017	Lagos, Nigeria	Prospective case-control study	20 / 20	creatinine mean = 54.90, sd = 21.73; eGFR mean = 130.24, sd = 42.57 [14]
Aloni et al. 2014	Kinshasa, D R Congo	Prospective case-control study	65 / 67	creatinine mean = 44.21, sd = 11.49; urea mean = 15.30, sd = 8.30; eGFR mean = 130.50, sd = 34.10 [6]
Asaolu et al. 2010	Ekiti, Nigeria	Prospective case-control study	42 / 42	creatinine mean = 10.55, sd = 8.13; urea mean = 10.50, sd = 6.28 [7]
Mohamed et al. 1992	Khartoum, Sudan	Prospective case-control study	84 / 28	creatinine mean = 22.20, sd = 4.00; urea mean = 22.70, sd = 5.70 [11]
El-Gamasy and El-Naghy 2019	Tanta, Egypt	Prospective case-control study	70 / 40	creatinine mean = 90.19, sd = 17.68; urea mean = 22.90, sd = 7.60 [8]
Okoro and Onwuameze 1991	Enugu, Nigeria	Prospective case-control study	60 / 305	eGFR mean = 111, sd = 36.0 [15]

eGFR estimated glomerular filtration rate

Risk of bias

ROBINS-E, a tool for assessing the risk of bias in non-randomized studies of exposure effects [42], was used to assess the risk of bias. Seven risks of bias domains were identified and assessed online using ROBINS-E. There were overall some concerns about the risk of bias, as shown in Fig. 2, details in Supplementary file 3.

Most studies (10 out of 17) reported statistically significant differences between the people with SCD (HbSS) (exposed participants) and controls (HbAA). There were

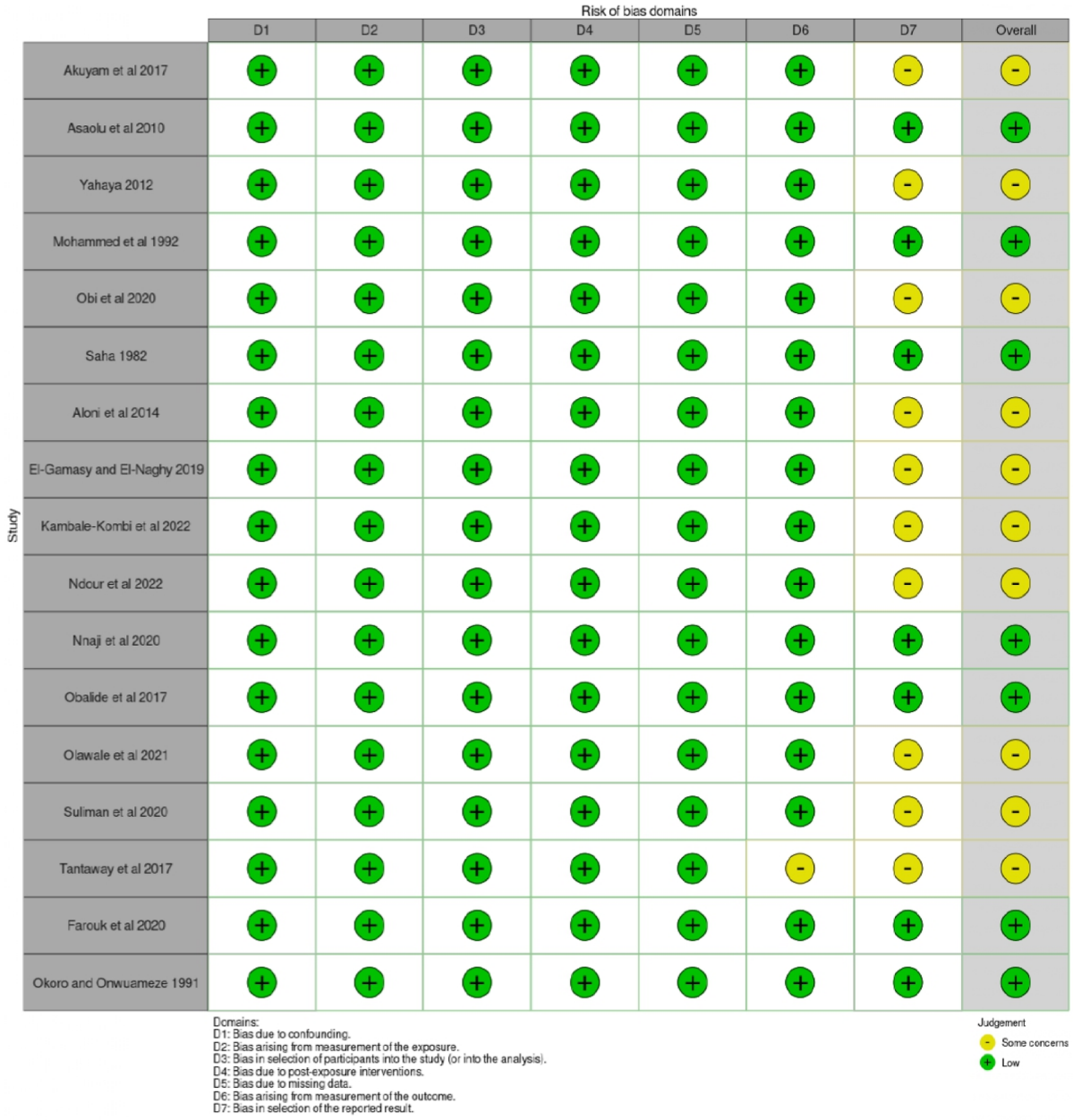

Fig. 2 Assessment of risk of bias of non-randomized studies of exposure effects using ROBINS-E [42]

some concerns about the risk of bias, as summarized in Fig. 2 above.

Liver function in people with sickle cell disease in Africa

The studies [7, 11, 19–22] revealed that people with SCD in Africa were more likely to have elevated liver enzymes than controls. The studies considered serum aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) results from six and four studies, respectively [7, 11, 19–22], as shown in Table 1.

The finding showed that AST's random effect pooled mean difference was not statistically significant (MD = 8.62 IU/L, 95% CI − 2.99–20.23, I^2 = 97.0%, $p < 0.01$). However, most studies revealed that the people with SCD had a higher serum AST level than the control group. Notably, substantial heterogeneity ($I^2 > 50\%$) was found. The details are in Fig. 3.

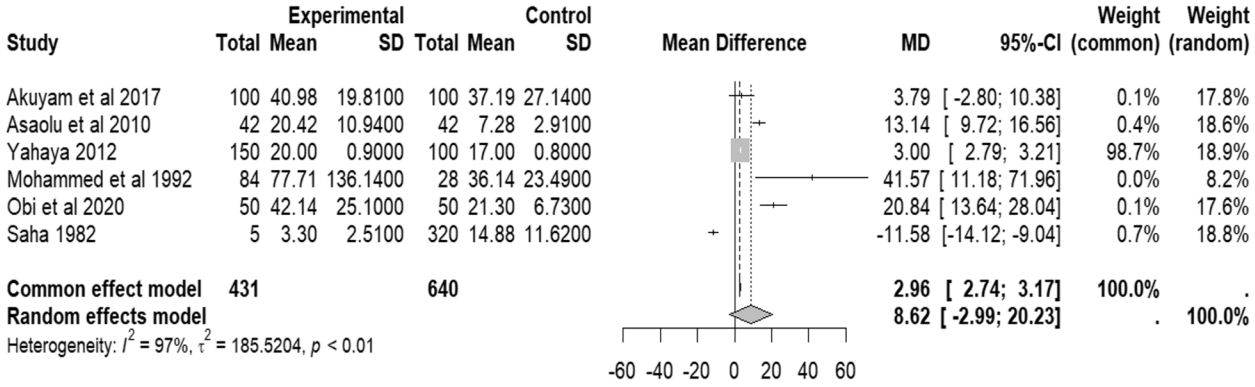

Fig. 3 Forest plot of serum AST of people with sickle cell disease compared to controls in Africa

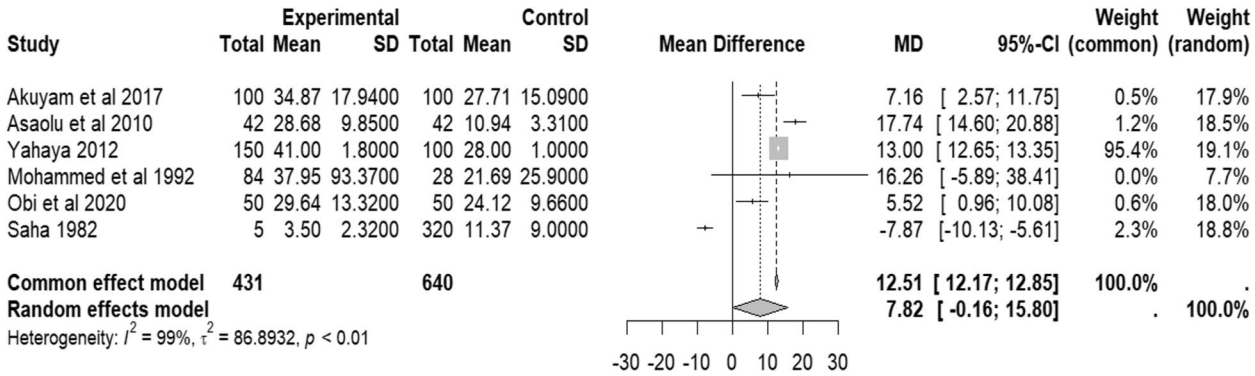

Fig. 4 Forest plot of serum ALT of people with sickle cell disease in Africa compared to controls

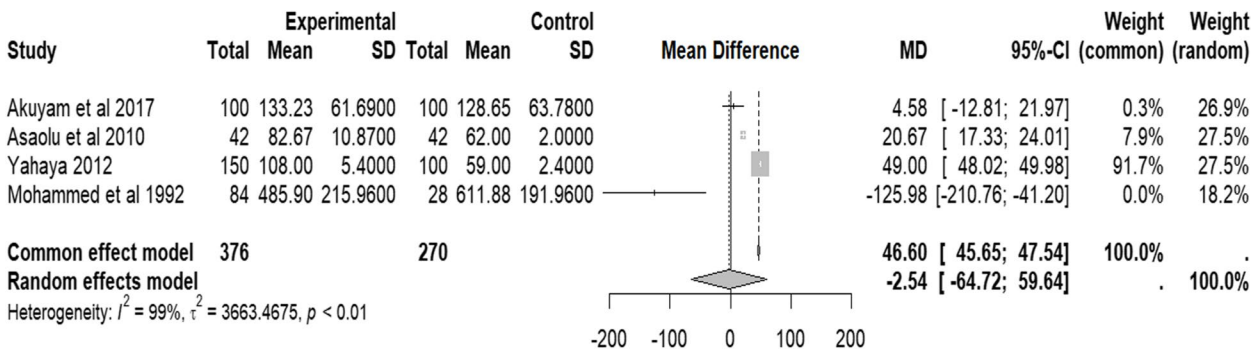

Fig. 5 Forest plot of serum ALP of people with sickle cell disease compared to controls in Africa

Similarly, the random effect of pooled mean difference (M.D.) of ALT was not statistically significant (MD = 7.82 IU/L, 95% CI − 0.16–15.58, I^2 = 99.0%, p < 0.01). The forest plot (Fig. 4) shows a higher serum ALT level among people with SCD than controls.

Findings from serum alkaline phosphatase (ALP) from four studies [7, 11, 19, 22] show a negative value of the random effect pooled mean difference (MD = − 2.54, 95% CI − 64.72–59.64, I^2 = 99.0%, p < 0.01 IU/L). This could have been due to one study (Mohammed et al. 1992) [11] that had a relatively high mean value of ALP in the control group; the details are in Fig. 5. Due to the small sample size, inferential analysis of bias was not performed.

Renal function in people with sickle cell disease in Africa

The studies [6–18] revealed that people with SCD in Africa may have a relatively compromised renal function. From the studies, three variables were used to evaluate the renal function in the study population, see Table 2.

The random effect pooled mean difference for serum creatinine from the eleven studies [6–8, 10–14, 16–18] is negative (MD = − 3.15, 95% CI − 15.02–8.72, I^2 = 99%, p < 0.01) units. The forest plot is skewed to the left of the experimental group, which may indicate increased creatinine clearance among people with SCD. Details are in Fig. 6.

In Fig. 7, the funnel plot shows only two studies under the "white" area, and the asymmetry was tested using Egger's regression. The finding suggested no statistically significant risk of bias (t = 1.09, df = 9, p = 0.305).

When the data of serum urea was considered, the random effect pooled mean difference from seven studies [6–8, 11, 12, 16, 17] was − 0.57 (95% CI − 3.49–2.36, I^2 = 99%, p < 0.01) units as can be seen in Fig. 8. Though not statistically significant, it may still show that people

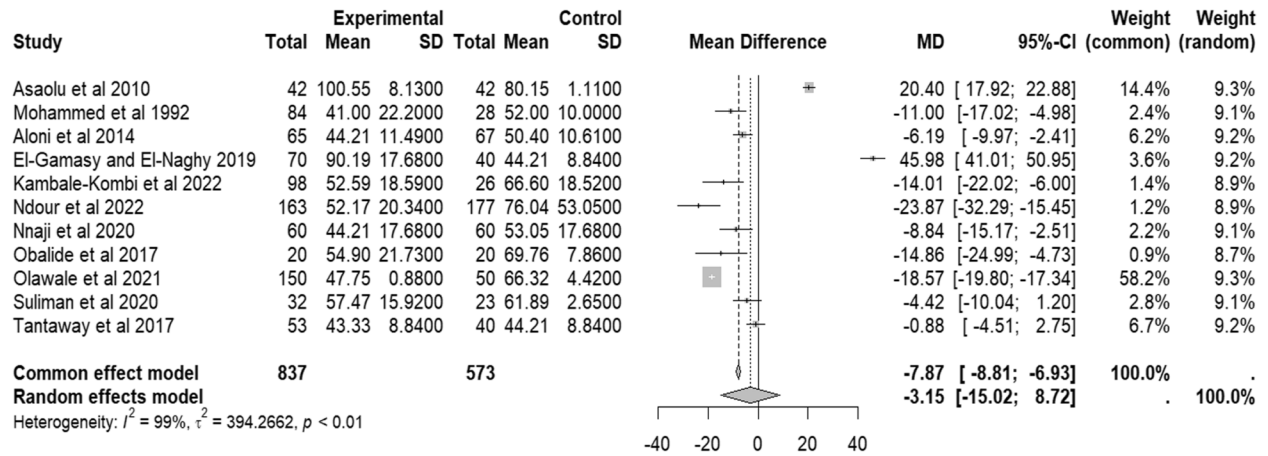

Fig. 6 Forest plot of serum creatinine for people with sickle cell disease compared to controls in Africa

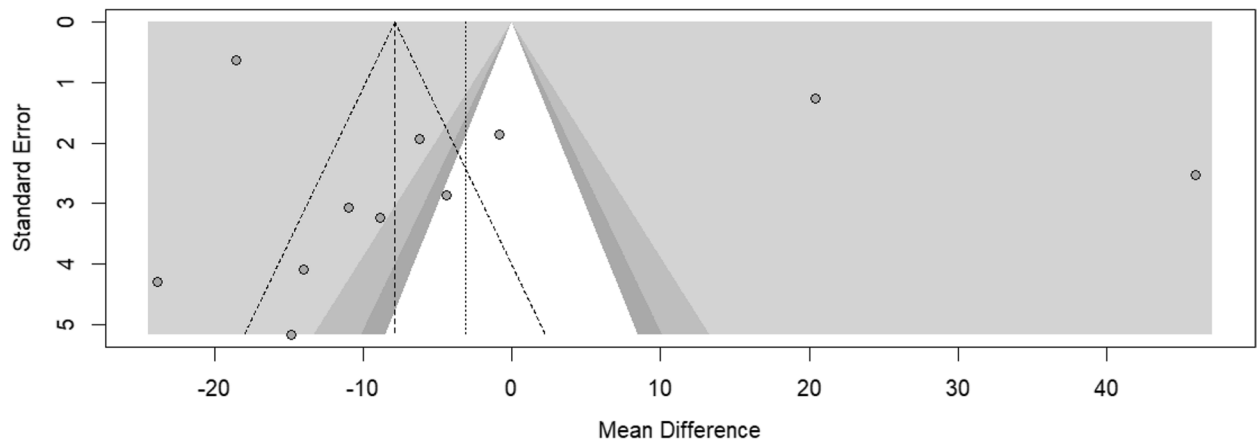

Fig. 7 Funnel plot of serum creatinine for people with sickle cell disease compared to controls in Africa

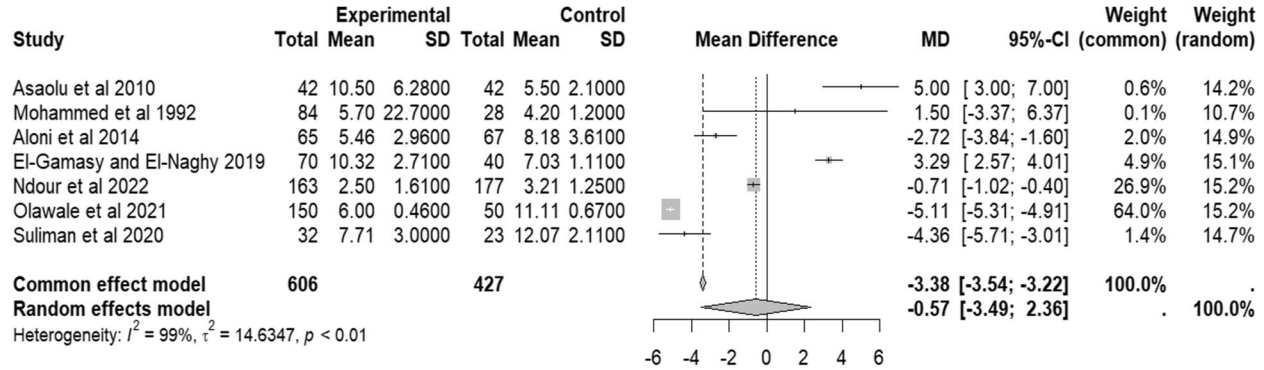

Fig. 8 Forest plot of serum urea of people with sickle cell disease compared to controls in Africa

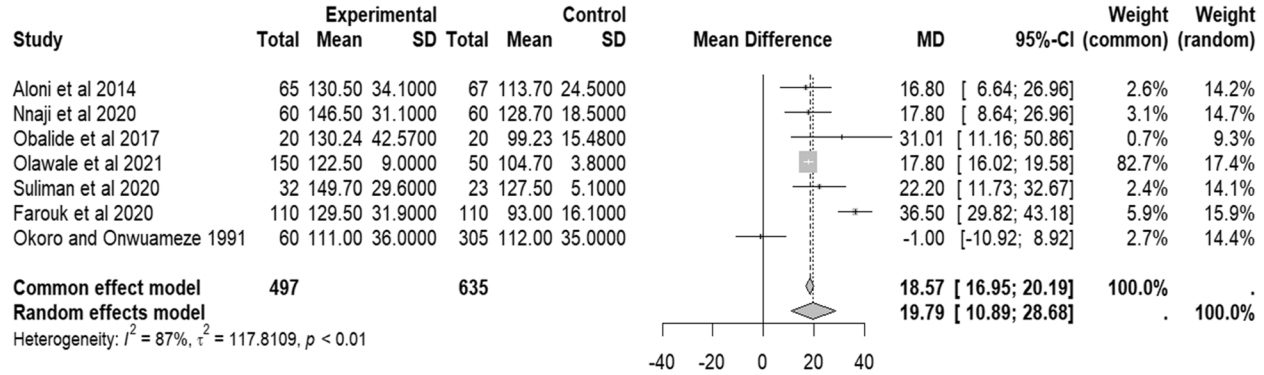

Fig. 9 Forest plot of eGFR of people with sickle cell disease compared to controls in Africa

with SCD have nearly similar serum urea levels to those of the control group.

Meanwhile, the random effect pooled mean difference of estimated glomerular filtration rate (eGFR) from seven studies [6, 9, 14–17] was positive (MD = 19.79, 95% CI 10.89–28.68 mL/min/1.73 m^2, $I^2 = 87.0\%$, $p < 0.01$). This demonstrates that people with sickle cell disease have higher eGFR (M.D. of estimated glomerular filtration > 0) than the control group. However, there was substantial heterogeneity ($I^2 > 50\%$). Details are in Fig. 9.

Discussion

This systematic review and meta-analysis found 17 articles from five African countries involving 1312 people with SCD (HbSS) and 1558 controls (HbAA). Compared to controls, there was no significant elevation of liver enzymes, urea, or creatinine among people with sickle cell disease.

The pooled mean difference of liver enzyme aspartate transaminase (AST) was 8.62 and alanine transaminase (ALT) was 7.82 above that of controls in this review. Normal levels of serum AST are 8–33 U/L, and ALT is less than 40 IU/L [44] and can rise to 2–3 times above normal levels in acute vaso-occlusive crises in sickle cell disease [45]. This was seen in a study in Pradesh, India [46], and the USA [45].

The pooled mean difference of serum alkaline phosphatase (ALP) in this review was -2.54 compared to controls. In acute hepatic sequestration [45] or bone disease [47], serum ALP may be elevated. However, the participants had a relatively lower serum ALP compared to controls. This may result from malnutrition and reduced dietary intake of zinc [48], and that cannot be excluded in these people with SCD in Africa.

The pooled mean difference for serum creatinine was − 3.15 while serum urea was − 0.57 compared to controls. The African population's low serum urea and creatinine may be linked to glomerular hyperfiltration [4]. In the USA, where people with SCD are treated with hydroxyurea for a long time, increased creatinine and urea levels were seen in renal failure typically after 23 years of age [49], a drug that was only recently introduced to sub-Saharan Africa [50]. The pooled mean difference of estimated glomerular filtration rate (eGFR) was 19.79 compared to controls. Serum creatinine is used to estimate glomerular filtration rate [51]. The

lower the serum creatinine level, the higher the eGFR [51].

Limitations and strengths of the study

Only 17 studies were found to have evaluated the liver and renal function tests in people with SCD in Africa and compared them to normal controls. Furthermore, most studies reported test results statistically significantly different from the controls. SCD vaso-occlusive crises insidiously affect the patients' organs with repeated attacks as they age. However, different studies included participants of different age groups and perhaps lifestyles, which could have affected the test results. With all the heterogeneity (I^2) > 50%, there was substantial variation in the reported articles' results. Nonetheless, this systematic review forms a baseline for future research on SCD in Africa.

Conclusion

This review found non-significantly elevated liver enzymes. Glomerular filtration rates were higher in people with SCD than in controls. More extensive prospective studies are recommended to investigate further the impact of SCD on renal and liver function.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02662-6.

Supplementary Material 1. Literature search strategy.

Supplementary Material 2. Records of the excluded studies.

Supplementary Material 3. Risk of bias.

Supplementary Material 4. Extracted data.

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Declared none.

Authors' contributions
Silvia Awor drafted the research protocol, registered it in PROSPERO, did data screening processes, and drafted the manuscript. Benard Abola did the meta-analysis and reviewed the manuscript. Felix Bongomin provided expert advice on the subject, did data screening, and reviewed the manuscript. Mark Mohan Kaggwa did data extraction and reviewed the manuscript. Francis Pebolo Pebalo proofread and reviewed the manuscript. David Musoke, Proscovia Nnamuyomba, Jackline Epila, Maxwell Malinga, Acaye Ongwech, and Christine Oryema guided the protocol writing and reviewed the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no conflicts of interest.

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