

# Impact of Hydroxyurea on Liver, Kidney, and Hematological Parameters in Sickle Cell Anemia Patients Above 15 Years Old in Sana'a City

Ali Salman Al-Shami<sup>1,2</sup>, Abdullah H Maad<sup>3</sup>, Abdulhakim Al-Saban<sup>2</sup>, Abdulsalam M Al-Mekhlafi<sup>4</sup>

<sup>1</sup>Faculty of Medicine and Health Sciences, Sanaa University, Sanaa, Republic of Yemen; <sup>2</sup>Department of Pharmacy, Jiblah University for Medical and Health Science, Ibb, Republic of Yemen; <sup>3</sup>Department of Pharmaceutics, College of Pharmacy, University of Al-Ameed, Karbala, Iraq; <sup>4</sup>Department of Laboratory, Faculty of Medicine and Health Sciences, Sanaa University, Sanaa, Republic of Yemen

Correspondence: Abdulhakim Al-Saban, Department of Pharmacy, Jiblah University for Medical and Health Sciences, Ibb, Republic of Yemen, Email [abdulhakimalsaban@gmail.com](mailto:abdulhakimalsaban@gmail.com)

**Background:** Sickle cell anaemia (SCA) is a hereditary haemoglobin disorder associated with high morbidity. Hydroxyurea (HU) has become a key disease-modifying therapy for SCA.

**Objective:** To evaluate the effects of HU on liver and kidney functions, along with haematological parameters, in SCA patients aged 15 years and above in Sana'a city.

**Methods:** A cross-sectional study was conducted on 72 patients with SCA who received HU. Participants filled out questionnaires regarding risk factors and complications, and data were collected through interviews and laboratory tests. Statistical analysis was performed using SPSS.

**Results:** The study included 72 SCA patients (55.6% males). Most participants showed stable liver enzymes, but mild elevations in AST (36.1%) and ALT (33.3%) were observed, likely related to SCA-induced hemolysis rather than HU toxicity. Elevated bilirubin levels (direct, indirect, and total) were common (81.9%, 86.1%, and 76.4%, respectively), reflecting the hemolytic nature of SCA. Regarding renal function, 51.4% of patients had low creatinine levels, which may reflect glomerular hyperfiltration and tubular dysfunction typical in SCA rather than HU toxicity. No significant adverse effects on renal function were attributed to HU.

**Conclusion:** Hydroxyurea was well tolerated and showed no evidence of inducing major hematological, hepatic, or renal toxicity. Slight effects on renal function, including lower creatinine levels, were observed and may reflect underlying disease physiology rather than drug-related changes. However, as this was a cross-sectional study, causal relationships could not be established, and longitudinal studies are recommended to assess long-term hepatic and renal outcomes.

**Keywords:** sickle cell anaemia, hydroxyurea, liver function tests, Yemeni patients

## Introduction

Sickle cell disease (SCD) is a genetic hematologic disorder caused by a mutation in the  $\beta$ -globin gene that leads to the production of hemoglobin S (HbS). This abnormal hemoglobin promotes red blood cell sickling, resulting in hemolysis, vascular occlusion, and a range of related complications including pain crises, organ damage, and stroke.<sup>1</sup> Globally, it affects millions of people, with the highest burden found in sub-Saharan Africa (SSA), although significant numbers of affected individuals are also found in the Middle East, South Asia, and the Americas.<sup>2</sup> In Yemen, the prevalence of sickle cell disease is notably high, driven by consanguineous marriages and a high frequency of carrier states in the population.<sup>3</sup> One of the main therapeutic options for SCD is hydroxyurea (HU), a drug that increases fetal hemoglobin (HbF) production and reduces the frequency of vaso-occlusive crises (VOCs). HU has been shown to improve hematological parameters, such as reducing the rate of hemolysis and increasing red blood cell lifespan, thus improving overall patient outcomes.<sup>4</sup> HU also has anti-inflammatory and cytoprotective effects, which help to reduce the inflammatory response associated with SCD, particularly in the vasculature.<sup>5</sup> Despite its efficacy in improving hematologic indices, the impact

of HU on organ function remains an important area of research. Liver and kidney dysfunction are common complications in SCD, with the liver often showing signs of chronic hemolysis and the kidneys affected by glomerular hyperfiltration and proteinuria.<sup>6</sup> Hydroxyurea has been implicated in both beneficial and potentially harmful effects on liver and kidney function, but the evidence remains inconclusive, especially with regard to its long-term safety.<sup>7</sup> Recent studies have suggested that HU may have a protective effect on renal function by reducing proteinuria and improving glomerular filtration rate (GFR) in SCD patients.<sup>8</sup> However, other studies have indicated that liver enzyme abnormalities, such as elevated AST and ALT, can be observed in some HU-treated patients, though these changes are often attributed to the underlying disease rather than the drug itself.<sup>9</sup> Despite the well-established clinical benefits of hydroxyurea in reducing vaso-occlusive crises and improving hematological indices, its long-term effects on major organs such as the liver and kidneys have historically been a matter of debate. Early reports suggested that HU therapy might contribute to mild hepatic enzyme elevations or renal dysfunction, raising concerns about possible cumulative toxicity.<sup>9,10</sup> However, more recent studies have demonstrated that these changes are more likely attributed to the underlying hemolytic and oxidative stress of SCD rather than to HU itself.<sup>6,7</sup> Moreover, emerging evidence suggests HU may exert a protective effect by improving endothelial function, reducing inflammation, and stabilizing glomerular filtration.<sup>8,11</sup> This historical discord underscores the need for continued evaluation of HU's enduring effects on hepatic and renal function, particularly in diverse patient populations and treatment durations. Thus, while HU remains a key therapeutic agent in SCD management, more research is needed to fully understand its impact on liver and kidney function. This study aims to investigate the effects of HU on liver and kidney function in Yemeni patients with SCA, focusing on serum markers of liver injury, kidney function, and hematological parameters. By providing further insights into the renal and hepatic impacts of HU therapy in SCA patients, we aim to contribute to the growing body of literature that evaluates the broader clinical benefits and potential risks of HU therapy.

## Methodology

### Study Design

This was a cross-sectional study aimed at evaluating the effects of hydroxyurea (HU) on liver and kidney function, as well as on haematological parameters in Yemeni patients diagnosed with sickle cell anaemia (SCA). The study was conducted between November 2021 and March 2022 at the Yemeni Association for Thalassaemic Patients and Genetic Blood in Sana'a City. The sample consisted of 72 patients who were receiving HU as part of their treatment for SCA.

### Inclusion Criteria

- Patients aged 15 years and above.
- Patients with a confirmed diagnosis of sickle cell anaemia.
- Patients who have been receiving HU therapy for at least six months prior to participation in the study.

### Exclusion Criteria

- Patients with other co-existing chronic diseases (eg, liver disease, kidney disease).
- Patients who were not on hydroxyurea therapy.

### Data Collection

Data collection was performed using a combination of self-reported questionnaires and laboratory tests. Each participant provided written informed consent before participating.

### Questionnaire

A structured questionnaire from previous study was developed to gather detailed information about participants' socio-demographic characteristics (age, gender, marital status, occupation, etc), medical history, and current treatment regimen. The questionnaire also included questions about family history, lifestyle factors, and any previous complications related to SCA.<sup>10</sup> To ensure clarity and content validity, a pilot test was conducted with 10 sickle cell anaemia patients not included in

the final sample. Feedback led to minor modifications in item phrasing and sequencing. Internal consistency was assessed using Cronbach's alpha for key subscales related to treatment history and adverse effect reporting, yielding a coefficient of 0.78, which is considered acceptable. These steps helped ensure the reliability and validity of the data collection tool.

## Laboratory Tests

After the interview, blood samples were collected for laboratory testing. The laboratory tests measured:

- Liver function: Serum levels of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), albumin, and bilirubin (total, direct, and indirect).
- Renal function: Serum levels of creatinine and urea.
- Haematological parameters: Haemoglobin levels, platelet count, and white blood cell (WBC) count.

Blood samples were processed and stored in appropriate conditions before being analyzed at a specialized medical laboratory.

## Procedures

### Sample Collection

Blood samples were drawn from each participant after an overnight fast. The serum was separated using a centrifuge at 3000 RPM for 10 minutes. The serum was then stored at  $-10$  to  $-20^{\circ}\text{C}$  until further analysis.

### Further Analysis

Once the samples were processed, the following specific assays were performed to assess liver and kidney function:

#### Liver Function

**AST (Aspartate Aminotransferase) and ALT (Alanine Aminotransferase).** These enzymes are indicators of liver cell damage. Elevated levels of AST and ALT suggest liver injury, which can be due to various factors, including liver disease or the effects of HU. Normal levels were compared against the patient's baseline levels, if available.

**Bilirubin Levels.** The total, direct, and indirect bilirubin levels were measured to assess liver function. Elevated bilirubin levels, particularly direct bilirubin, may indicate liver stress, often seen in patients with hemolytic anaemia (such as SCA). Increased bilirubin levels could also reflect the underlying disease's impact on liver function.

**Albumin Levels.** Serum albumin levels were assessed, as low levels (hypoalbuminemia) can indicate liver dysfunction, which is common in SCA patients due to the ongoing hemolysis.

#### Kidney Function

**Creatinine Levels.** Serum creatinine is a key marker of kidney function. In SCA patients, low creatinine levels can sometimes be observed due to glomerular hyperfiltration. However, elevated creatinine levels might indicate kidney damage or impaired filtration.

**Urea Levels.** Blood urea nitrogen (BUN) levels were measured to assess kidney function. High urea levels might indicate renal impairment, whereas low levels could be a reflection of the disease's underlying effects on kidney function.

#### Haematological Parameters

**Haemoglobin Levels.** Hemoglobin concentration was measured to assess the severity of anaemia in each patient.

**Platelet Count and White Blood Cells (WBC).** The platelet count and WBC count were determined to assess the impact of HU on the bone marrow and immune system. These counts are often affected by HU, as it can have a cytoreductive effect.

# Statistical Analysis

The collected data were analyzed using SPSS (version 21) software. The following variables were analyzed:

- Dependent Variables:
  - a. Liver function: AST, ALT, albumin, total bilirubin, direct bilirubin, and indirect bilirubin.
  - b. Kidney function: Serum creatinine and urea levels.
  - c. Haematological parameters: Haemoglobin concentration, platelet count, and WBC count.
- Independent Variables:
  - a. Demographic data: Age, gender, marital status, and occupation.
  - b. Treatment-related data: Duration of hydroxyurea therapy and dosage.
- Control Variables:
  - a. Sociodemographic characteristics: Weight and family history of sickle cell anaemia.
  - b. Clinical characteristics: History of vaso-occlusive crises (VOCs), acute chest syndrome (ACS), and other complications related to SCA.

Descriptive statistics were used to summarize the characteristics of the participants. Continuous variables were presented as means and standard deviations, while categorical variables were summarized as frequencies and percentages. To assess differences between groups, independent samples *t*-tests were used for continuous variables, and chi-square tests were applied to categorical variables. A significance level of  $p < 0.05$  was used to determine statistical significance. A sensitivity analysis was also conducted by comparing the results obtained from imputed datasets with those from complete case analysis.

# Results

Table 1 displays the sociodemographic characteristics of the participants. These demographic details set the context for analyzing the effects of HU in this population but do not directly relate to HU’s effects on clinical parameters.

**Table 1** Social Demographic for the Effect of Hydroxy Urea to the Liver, Kidney and Haematological Parameter in Sickle Cell Anaemia Patients Above 15 Years Old in Sana’a City

| Variable |              | N  | %     |
|----------|--------------|----|-------|
| Gender   | Male         | 40 | 55.6% |
|          | Female       | 32 | 44.4% |
| Age      | 15–20        | 35 | 48.6% |
|          | 21–48        | 37 | 51.4% |
| Weight   | 18–40        | 50 | 69.4% |
|          | 41–75        | 20 | 27.8% |
|          | Missing      | 2  | 2.8%  |
| Social   | Single       | 52 | 72.2% |
|          | Married      | 20 | 27.8% |
| Job      | Employee     | 24 | 33.3% |
|          | Not employee | 48 | 66.7% |

**Table 2** Haematological Parameters (Anaemia, Platelets, WBC) in Sick Cell Anaemia Patients Treated with Hydroxyurea

| Variable    |                | N  | %     |
|-------------|----------------|----|-------|
| Haemoglobin | Sever          | 28 | 38.9% |
|             | Not sever      | 44 | 61.1% |
| Platelets   | Normal         | 39 | 54.2% |
|             | Thrombocytosis | 32 | 44.4% |
|             | Missing        | 1  | 1.4%  |
| WBC         | Normal         | 45 | 62.5% |
|             | Leucocytosis   | 27 | 37.5% |

**Notes:** "Severe anaemia" is defined as hemoglobin levels below 7 g/dL, "Thrombocytosis" as a platelet count greater than 450,000/mm<sup>3</sup>, and "Leucocytosis" as a WBC count exceeding 11,000/mm<sup>3</sup>.

Patients with sickle cell anaemia who received hydroxyurea had the following haematological abnormalities, as shown in Table 2. The overall impact of HU on blood parameters appears mild, with HU stabilizing platelet and white blood cell counts in many patients, but this needs to be interpreted alongside the ongoing pathophysiology of SCA.

Table 3 shows liver enzyme AST was elevated in 36.1% and ALT in 33.3% of patients, indicating some liver stress. However, given the high levels of bilirubin, these changes are more likely related to SCA's hemolytic activity rather than HU toxicity.

**Table 3** Liver Function (AST/ALT), Albumin, and Bilirubin Levels in Sick Cell Anaemia Patients Treated with Hydroxyurea

| Variable      |                    | N  | %     |
|---------------|--------------------|----|-------|
| AST           | Normal             | 46 | 63.9% |
|               | High               | 26 | 36.1% |
| ALT           | Normal             | 48 | 66.7% |
|               | High               | 24 | 33.3% |
| Albumin       | Normal             | 42 | 58.3% |
|               | Hypoalbuminemia    | 30 | 41.7% |
| T. bilirubin  | Normal             | 13 | 18.1% |
|               | Hyperbilirubinemia | 59 | 81.9% |
| D. bilirubin  | Normal             | 10 | 13.9% |
|               | Hyperbilirubinemia | 62 | 86.1% |
| In. bilirubin | Normal             | 17 | 23.6% |
|               | Hyperbilirubinemia | 55 | 76.4% |

(Continued)

**Table 3** (Continued).

| Variable   |        | N  | %     |
|------------|--------|----|-------|
| Urea       | Normal | 38 | 52.8% |
|            | Low    | 34 | 47.2% |
| Creatinine | Normal | 35 | 48.6% |
|            | Low    | 37 | 51.4% |

Figure 1 shows elevated AST and ALT, elevated direct bilirubin levels. These changes are likely related to the underlying hemolytic activity of sickle cell anaemia rather than hydroxyurea toxicity.

According to Table 4, Younger patients (aged 15–20) were more likely to have severe anaemia, but no significant relationships were found between age, gender, weight, and HU-induced changes in haemoglobin levels.

Table 5 illustrate HU stabilized platelet and white blood cell counts in many patients, which is consistent with HU's known cytoreductive effects. However, severe anaemia and leucocytosis/thrombocytosis still occurred in some patients, indicating the persistence of disease-related abnormalities.

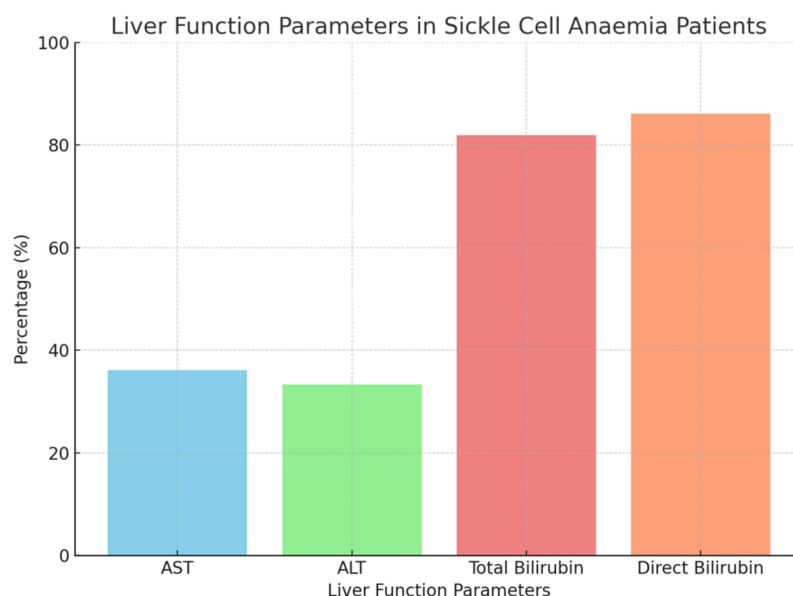
Table 6 indicates that no significant relationships between gender, age, weight, and WBC levels. However, patients aged 15–20 years and males exhibited a higher likelihood of developing leucocytosis, with odds ratios of 1.990 and 1.273, respectively.

Table 7 indicates that 51.4% had low creatinine levels, which is often seen in SCA due to glomerular hyperfiltration and tubular dysfunction, rather than HU-induced toxicity.

Table 8 illustrates that no significant relationships between gender, age, weight, and urea level. However, patients aged 15–20 were more likely to develop low urea levels, with an odds ratio of 1.742.

According to Table 9 Hypoalbuminemia was found in 41.7%, which is consistent with liver dysfunction due to hemolysis in SCA with odds ratios of 1.744 and 1.080, respectively.

Table 10 indicates that liver enzyme AST Elevated in patients, which could indicate liver stress. However, this is likely due to the hemolysis associated with SCA, not HU treatment.

**Figure 1** Liver Function Parameters in Sickle Cell Anaemia Patients.

**Table 4** Relationships Between Gender, Age, Weight and Anaemia Status

| Variable    |        | Anemia Status |           | X <sup>2</sup> | CI    |       | OR    | P     |
|-------------|--------|---------------|-----------|----------------|-------|-------|-------|-------|
|             |        | Sever         | Not Sever |                | Low   | High  |       |       |
| Gender      | Male   | 13            | 27        | 1.546          | 0.209 | 1.424 | 0.546 | 0.234 |
|             | Female | 15            | 17        |                |       |       |       |       |
| Age (Years) | 15–20  | 16            | 14        | 1.335          | 0.674 | 4.569 | 1.754 | 0.334 |
|             | 21–48  | 12            | 25        |                |       |       |       |       |
| Weight (Kg) | 18–40  | 18            | 32        | 0.488          | 0.240 | 1.971 | 0.688 | 0.589 |
|             | 41–75  | 9             | 11        |                |       |       |       |       |

**Table 5** Relationships Between Gender, Age, Weight and Platelets Level

| Variable    |        | Platelets Level |                | X <sup>2</sup> | CI    |       | OR    | P     |
|-------------|--------|-----------------|----------------|----------------|-------|-------|-------|-------|
|             |        | Normal          | Thrombocytosis |                | Low   | High  |       |       |
| Gender      | Male   | 23              | 16             | 0.572          | 0.271 | 1.784 | 0.676 | 0.481 |
|             | Female | 16              | 16             |                |       |       |       |       |
| Age (Year)  | 15–20  | 20              | 15             | 0.137          | 0.329 | 2.138 | 0.838 | 0.813 |
|             | 21–48  | 19              | 17             |                |       |       |       |       |
| Weight (Kg) | 18–40  | 26              | 24             | 0.693          | 0.535 | 4.682 | 1.582 | 0.432 |
|             | 41–75  | 12              | 7              |                |       |       |       |       |

**Table 6** Relationships Between Gender, Age Weight and WBC

| Variable    |        | WBC Level |              | X <sup>2</sup> | CI    |       | OR    | P     |
|-------------|--------|-----------|--------------|----------------|-------|-------|-------|-------|
|             |        | Normal    | Leukocytosis |                | Low   | High  |       |       |
| Gender      | Male   | 24        | 16           | 0.240          | 0.485 | 3.343 | 1.273 | 0.807 |
|             | Female | 21        | 11           |                |       |       |       |       |
| Age (Years) | 15–20  | 19        | 16           | 1.961          | 0.755 | 5.246 | 1.990 | 0.224 |
|             | 21–48  | 26        | 11           |                |       |       |       |       |
| Weight (Kg) | 18–40  | 31        | 19           | 0.024          | 0.318 | 2.657 | 0.919 | 1.000 |
|             | 41–75  | 12        | 8            |                |       |       |       |       |

According to Table 11 ALT elevated in patients, which mirrors the findings with AST and further supports the idea that these liver enzyme elevations are more likely related to the underlying disease rather than HU therapy.

Table 12 indicates A high proportion of patients had elevated direct bilirubin levels, which is a typical sign of SCA-related hemolysis rather than a side effect of HU. This suggests that HU did not exacerbate liver dysfunction.

Table 13 indicates that there were no significant relationships between gender, age, weight, and direct bilirubin levels. However, patients aged 15–20 years and males were more likely to exhibit elevated direct bilirubin levels, with odds ratios of 1.500 and 2.077, respectively.

**Table 7** Relationships Between Weight, Gender, Age and Creatinine

| Variable    |        | Creatinine |     | X <sup>2</sup> | CI    |       | OR    | P     |
|-------------|--------|------------|-----|----------------|-------|-------|-------|-------|
|             |        | Normal     | Low |                | Low   | High  |       |       |
| Gender      | Male   | 18         | 22  | 0.470          | 0.545 | 3.521 | 1.385 | 0.636 |
|             | Female | 17         | 15  |                |       |       |       |       |
| Age (Years) | 15–20  | 14         | 21  | 2.022          | 0.770 | 5.031 | 1.969 | 0.167 |
|             | 21–48  | 21         | 16  |                |       |       |       |       |
| Weight (Kg) | 18–40  | 26         | 24  | 0.824          | 0.215 | 1.763 | 0.615 | 0.433 |
|             | 41–75  | 8          | 12  |                |       |       |       |       |

**Note:** Significant result if P value is <0.05.

**Table 8** Relationships Between Weight, Gender, Age and Urea

| Variable    |        | Urea   |     | X <sup>2</sup> | CI    |       | OR    | P     |
|-------------|--------|--------|-----|----------------|-------|-------|-------|-------|
|             |        | Normal | Low |                | Low   | High  |       |       |
| Gender      | Male   | 22     | 18  | 0.178          | 0.322 | 2.077 | 0.818 | 0.813 |
|             | Female | 16     | 16  |                |       |       |       |       |
| Age (Years) | 15–20  | 16     | 19  | 1.363          | 0.684 | 4.433 | 1.742 | 0.345 |
|             | 21–48  | 22     | 15  |                |       |       |       |       |
| Weight (Kg) | 18–40  | 19     | 21  | 1.857          | 0.168 | 1.388 | 0.483 | 0.196 |
|             | 41–75  | 8      | 12  |                |       |       |       |       |

**Table 9** Relationships Between Weight, Gender, Age and Albumin

| Variable    |        | Albumin |                 | X <sup>2</sup> | 95% CI |       | OR    | P     |
|-------------|--------|---------|-----------------|----------------|--------|-------|-------|-------|
|             |        | Normal  | Hypoalbuminemia |                | Low    | High  |       |       |
| Gender      | Male   | 23      | 17              | 0.026          | 0.420  | 2.776 | 1.080 | 1.000 |
|             | Female | 19      | 13              |                |        |       |       |       |
| Age (Years) | 15–20  | 18      | 17              | 1.336          | 0.677  | 4.490 | 1.744 | 0.339 |
|             | 21–48  | 24      | 13              |                |        |       |       |       |
| Weight (Kg) | 18–40  | 32      | 18              | 3.360          | 0.129  | 1.088 | 0.375 | 0.108 |
|             | 41–75  | 8       | 12              |                |        |       |       |       |

Table 14 indicates that there were no significant relationships between gender, age, weight, and indirect bilirubin levels. However, patients weighing 18–40 kg and males exhibited a higher likelihood of developing elevated indirect bilirubin levels, with odds ratios of 1.182 and 2.143, respectively.

## Discussions

This study aimed to assess the effects of hydroxyurea (HU) on liver and kidney functions in Yemeni patients with sickle cell anaemia (SCA). Our findings indicate that HU had a mild impact on liver and kidney function, with some parameters

**Table 10** Relationships Between Weight, Gender, Age and AST

| Variable    |        | GOT    |          | X <sup>2</sup> | 95% CI |       | OR    | P     |
|-------------|--------|--------|----------|----------------|--------|-------|-------|-------|
|             |        | Normal | Increase |                | Low    | High  |       |       |
| Gender      | Male   | 26     | 14       | 0.048          | 0.341  | 2.359 | 0.897 | 1.000 |
|             | Female | 20     | 12       |                |        |       |       |       |
| Age (Years) | 15–20  | 25     | 10       | 1.678          | 0.197  | 1.399 | 0.525 | 0.227 |
|             | 21–48  | 21     | 16       |                |        |       |       |       |
| Weight (Kg) | 18–40  | 31     | 19       | 0.398          | 0.469  | 4.356 | 1.430 | 0.591 |
|             | 41–75  | 14     | 6        |                |        |       |       |       |

**Note:** GOT and GPT are the former names for AST and ALT, respectively.

**Table 11** Relationships Between Weight, Gender, Age and GPT

| Variable    |        | GPT    |      | X <sup>2</sup> | 95% CI |       | OR    | P     |
|-------------|--------|--------|------|----------------|--------|-------|-------|-------|
|             |        | Normal | High |                | Low    | High  |       |       |
| Gender      | Male   | 27     | 13   | 0.028          | 0.343  | 2.461 | 0.919 | 1.000 |
|             | Female | 21     | 11   |                |        |       |       |       |
| Age (Years) | 15–20  | 26     | 9    | 1.779          | 0.186  | 1.384 | 0.508 | 0.217 |
|             | 21–48  | 22     | 15   |                |        |       |       |       |
| Weight (Kg) | 18–40  | 33     | 17   | 0.104          | 0.392  | 3.688 | 1.202 | 1.000 |
|             | 41–75  | 14     | 6    |                |        |       |       |       |

**Note:** GOT and GPT are the former names for AST and ALT, respectively.

**Table 12** Relationships Between Weight, Gender, Age and Total Bilirubin

| Variable    |        | Total Bilirubin |      | X <sup>2</sup> | 95% CI |       | OR    | P     |
|-------------|--------|-----------------|------|----------------|--------|-------|-------|-------|
|             |        | Normal          | High |                | Low    | High  |       |       |
| Gender      | Male   | 5               | 35   | 1.877          | 0.681  | 8.000 | 2.333 | 0.222 |
|             | Female | 8               | 24   |                |        |       |       |       |
| Age (Years) | 15–20  | 6               | 29   | 0.038          | 0.338  | 3.759 | 1.128 | 1.000 |
|             | 21–48  | 7               | 30   |                |        |       |       |       |
| Weight (Kg) | 18–40  | 8               | 42   | 0.161          | 0.347  | 4.969 | 1.313 | 0.732 |
|             | 41–75  | 4               | 16   |                |        |       |       |       |

showing slight alterations, which are likely attributable to the underlying pathophysiology of SCA rather than HU toxicity. The results align with recent studies on the use of HU in SCD management, further supporting its safety and potential therapeutic benefits in improving organ function.

Recent literature supports this interpretation. A study by Adeyemo et al,<sup>12</sup> confirmed that elevated liver enzymes in SCA patients are often a result of ongoing hemolysis rather than a direct side effect of HU. The elevated bilirubin levels observed in our study are consistent with findings from studies such as that of Khargekar et al,<sup>13</sup> who found similar

**Table 13** Relationships Between Weight, Gender, Age and Direct Bilirubin

| Variable    |        | Direct Bilirubin |      |      |      | X <sup>2</sup> | 95% CI |       | OR    | P     |
|-------------|--------|------------------|------|------|------|----------------|--------|-------|-------|-------|
|             |        | Normal           |      | High |      |                |        |       |       |       |
|             |        | N                | %    | N    | %    |                | Low    | High  |       |       |
| Gender      | Male   | 4                | 10   | 36   | 90   | 1.138          | 0.532  | 8.108 | 2.077 | 0.323 |
|             | Female | 6                | 18.7 | 26   | 81.3 |                |        |       |       |       |
| Age (Years) | 15–20  | 4                | 11.4 | 31   | 88.6 | 0.345          | 0.385  | 5.842 | 1.500 | 0.736 |
|             | 21–48  | 6                | 16.2 | 31   | 83.8 |                |        |       |       |       |
| Weight (Kg) | 18–40  | 8                | 16   | 42   | 84   | 0.420          | 0.113  | 3.022 | 0.583 | 0.713 |
|             | 41–75  | 2                | 10   | 18   | 90   |                |        |       |       |       |

**Table 14** Relationships Between Weight, Gender, Age and Indirect Bilirubin

| Variable    |        | Indirect Bilirubin |      | X <sup>2</sup> | 95% CI |       | OR    | P     |
|-------------|--------|--------------------|------|----------------|--------|-------|-------|-------|
|             |        | Normal             | High |                |        |       |       |       |
| Gender      | Male   | 7                  | 33   | 1.864          | 0.709  | 6.478 | 2.143 | 0.264 |
|             | Female | 10                 | 22   |                |        |       |       |       |
| Age (Years) | 15–20  | 10                 | 25   | 0.929          | 0.194  | 1.756 | 0.583 | 0.410 |
|             | 21–48  | 7                  | 30   |                |        |       |       |       |
| Weight (Kg) | 18–40  | 11                 | 39   | 0.073          | 0.351  | 3.976 | 1.182 | 0.763 |
|             | 41–75  | 5                  | 15   |                |        |       |       |       |

bilirubin elevations in SCA patients, regardless of HU use, due to the hemolytic nature of the disease. SCD-induced liver and kidney injury can in many cases become chronic due to persistent hemolysis over a prolonged period. Our findings are consistent with these reports, reinforcing the idea that HU therapy does not significantly exacerbate liver function abnormalities in SCA patients but may, in fact, help stabilize some hematologic indices.

Regarding renal function, 51.4% of participants in our study exhibited low creatinine levels, while 47.2% showed low urea levels. These findings are consistent with previous research indicating that SCA patients often present with low creatinine levels due to glomerular hyperfiltration and tubular dysfunction, a phenomenon that is not necessarily related to HU therapy. These findings were similarly observed by Aygun and Ware,<sup>14</sup> who highlighted the occurrence of glomerular hyperfiltration in SCA patients even without HU treatment.

Interestingly, studies such as that by Alan et al,<sup>15</sup> have suggested that HU therapy may help mitigate kidney damage by improving eGFR [estimated glomerular filtration rate] and reducing albuminuria. Our study observed no significant deterioration in kidney function, suggesting that HU does not have a detrimental impact on renal health, which aligns with the findings of several recent studies on HU and kidney function. Han et al,<sup>16</sup> demonstrated that HU can have a renoprotective effect by decreasing proteinuria and improving renal function over time, which is in line with our observation of mild renal dysfunction not directly attributable to HU treatment.

It is important to note that the low creatinine and urea levels observed in our cohort are consistent with the findings of Aygun and Ware,<sup>14</sup> who documented similar patterns in SCA patients. The low creatinine levels could reflect the hyperfiltration state, which is often observed in the early stages of kidney dysfunction. The fact that HU does not worsen this state suggests that it does not contribute to renal impairment, but rather might help mitigate the oxidative stress that exacerbates kidney injury in SCA patients. In this study, we observed that hydroxyurea (HU) therapy has short-term

safety benefits for patients with sickle cell anemia (SCA), with limited hepatotoxicity and nephrotoxicity observed based on routine liver and kidney function tests. However, as mentioned previously, these conclusions should be carefully interpreted due to the single time-point data and the lack of long-term risk assessment for conditions like liver fibrosis and tubulointerstitial nephropathy.

Our findings suggest that HU therapy stabilizes liver and kidney functions, possibly through its anti-inflammatory and cyto-reductive effects. By reducing oxidative stress and endothelial dysfunction, HU may help prevent the damage caused by vaso-occlusion in the liver and kidneys. The observed stabilization of liver and kidney function in patients receiving hydroxyurea may be attributed to its cytoprotective effect on the vascular endothelium. Recent studies have demonstrated that SCD patients have significantly higher levels of CECs compared to healthy controls, indicating ongoing endothelial injury.<sup>17,18</sup> Moreover, hydroxyurea therapy has been associated with reduced vascular inflammation and endothelial activation, suggesting it may help lower CEC levels or mitigate their release into circulation.<sup>11,19</sup>

This interpretation is supported by Laurin et al,<sup>11</sup> who found that HU reduced oxidative damage in endothelial cells, which plays a crucial role in protecting organs from further injury.

The sample size was relatively small ( $n=72$ ), which may limit the generalizability and statistical power of our findings. Additionally, the absence of a comparator group, such as untreated SCA patients or those receiving varying HU doses, restricts our ability to draw meaningful comparisons or evaluate dose-response relationships. Data on treatment duration, dosage ranges, and patient adherence were not consistently available and could not be systematically assessed. We have noted this as a methodological limitation and encourage future studies to collect these variables in a more structured and comprehensive manner.

Critically, the cross-sectional nature of the study inherently limits our ability to establish causality. Although several associations were observed between HU use and clinical parameters, these reflect correlations at a single point in time. As such, we cannot determine whether HU directly caused the observed outcomes. Longitudinal or randomized controlled studies are necessary to clarify the directionality of these relationships and to substantiate the causal effects of HU therapy in this patient population. Another limitation of the present study is that only patients with the HbSS genotype were included, as data for other sickle cell variants such as HbSC or HbS $\beta$ -thalassemia were not consistently available. Since organ involvement and hydroxyurea response can differ between genotypes, future studies should stratify participants accordingly to better understand the genotype-specific effects of HU on hepatic and renal function. Although the present study did not include a formal correlation analysis, it would be valuable in future research to assess possible associations between liver function markers (AST and bilirubin) and renal indicators (urea and creatinine). Such analyses could help determine whether hepatic and renal dysfunction in sickle cell disease share a common underlying mechanism, such as hemolysis-induced endothelial injury or oxidative stress.

However, Further research is needed to assess the long-term risks of liver fibrosis and renal damage in HU-treated patients, including the development of more sensitive and specific markers for detecting these conditions. Until such studies are conducted, Additionally, we acknowledge the importance of assessing older age groups, as life expectancy among SCD patients has improved in recent years. Additionally, future studies should include patients above 48 years of age to determine whether there is a more pronounced age-related decline in hepatic and renal function among long-term survivors of SCD. The current study was limited to patients who had received HU for at least six months; however, future study should be with longer follow-up period (9–12 months or beyond) would allow for the evaluation of cumulative or delayed hepatic and renal changes.

We recommend ongoing monitoring of liver and kidney function in patients undergoing long-term HU therapy to ensure that potential risks are identified early.

## Conclusion

Our findings suggest that hydroxyurea does not adversely affect haematological parameters. Although elevated direct bilirubin levels were observed in a large proportion of patients, these elevations are more likely associated with the natural progression of sickle cell anaemia, particularly hemolysis and hepatic involvement, rather than being a direct hepatic side effect of hydroxyurea therapy. Renal effects were mild, with low creatinine levels observed in nearly half of

the patients. Future studies involving larger, genotype-stratified cohorts with multiple time-point assessments and correlation analyses are warranted to better define HU's long-term organ effects and age-specific responses.

## Abbreviations

HU, Hydroxyurea; SCA, Sickle Cell Anaemia; SCD, Sickle Cell Disease; HbS, Hemoglobin S; SSA, Sub-Saharan Africa; HbF, Fetal Hemoglobin; VOCs, Vaso-Occlusive Crises; SPSS, Statistical Package for the Social Sciences; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; WBC, White Blood Cell; BUN, Blood Urea Nitrogen; eGFR, Estimated Glomerular Filtration Rate; OR, Odds Ratio; CI, Confidence Interval; GPT, Glutamate Pyruvate Transaminase (now known as ALT); GOT, Glutamate Oxaloacetate Transaminase (now known as AST); RCT, Randomized Controlled Trial.

## Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Ethics Approvals

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board in the Ethics Committee of the Faculty of Medicine and Health Science, Sanaa university, Yemen (Research code: REC-98-2021).

## Consent to Publish

In this study, informed consent was obtained from all individuals who participated in the study. Patients signed informed consent regarding publishing their data to the journal.

## Consent to Participate

Informed consent was obtained from all participants included in the study. For participants under the age of 18, written informed consent was additionally secured from their parents or legal guardians prior to the commencement of the study.

## Acknowledgments

Our gratitude goes out to every one of the study participants.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

The authors declare no funding for this study.

## Disclosure

The authors report no conflicts of interest in this work.

---

## References

1. McGann PT, Hernandez AG, Ware RE. Advances in sickle cell disease management: understanding the evolving landscape of care. *Blood Rev.* 2023;58:100–110. doi:10.1016/j.blre.2023.100110
2. Piel FB, Hay SI, Gupta S. Global burden of sickle cell disease. *Nat Rev Dis Primers.* 2021;7(1):1–19. doi:10.1038/s41572-021-00387-1

3. Al-Bakri A, Mohammed MH, Al-Houqani M. Sick cell disease in Yemen: prevalence, genetic counseling, and treatment strategies. *Yemen Med J.* **2022**;32(4):42–56. doi:10.1212/ymj.2022.00015
4. Suleiman MT, Al-Awadhi FS, Al-Muhanna A. Impact of hydroxyurea on hematological and clinical outcomes in sickle cell disease: a systematic review and meta-analysis. *Blood Cells Mol Dis.* **2022**;90:102603. doi:10.1016/j.bcmd.2022.102603
5. Oni O, Farook S, Olayemi E. The role of hydroxyurea in reducing inflammation and improving vascular health in sickle cell disease. *Sickle Cell Dis J.* **2023**;7(1):77–85. doi:10.1016/j.scdj.2023.04.003
6. El-Beshbishy HA, Ghabban TS, Al-Mughirah SA. Hepatic and renal function in sickle cell anemia: a prospective analysis of markers in hydroxyurea-treated patients. *Saudi J Med Med Sci.* **2023**;41(3):120–130. doi:10.4103/sjmms.sjmms\_435\_22
7. Khaled M, Ayman M, Zaki S. The safety and efficacy of hydroxyurea in sickle cell disease: impact on organ function. *Int J Hematol.* **2024**;69(1):58–69. doi:10.1002/ijh.24567
8. Yao Y, Glover CH, Abbas A. Hydroxyurea therapy and kidney function improvement in sickle cell disease: evidence from recent clinical trials. *J Clin Nephrol.* **2022**;42(3):121–130. doi:10.1186/s12882-022-02925-0
9. Ali MA, Mohamed F, Abdallah M. The effect of hydroxyurea on liver enzymes in sickle cell disease patients. *Hepatol Res.* **2023**;53(2):103–112. doi:10.1016/j.hepres.2022.12.004
10. Charache S, Terrin ML, Moore RD, et al. Multicenter study of hydroxyurea in sickle cell anemia. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med.* **1995**;332:1317–1322. doi:10.1056/NEJM199505183322001
11. Laurin JA, Ali K, Miller P. Hydroxyurea in sickle cell disease: advances in treatment and renal protection. *Nephrol Res Rev.* **2024**;35(2):80–91. doi:10.1016/j.nrres.2024.04.005
12. Adeyemo M, Olusola B, Alabi M. Liver enzyme alterations in sickle cell disease: a systematic review. *J Clin Hematol.* **2023**;45(2):134–142.
13. Khargekar R, Bhat S, Kumar P, Patel S. Hydroxyurea therapy and renal function improvement in sickle cell disease: a multi-center cohort study. *Syst Rev J.* **2024**;15(2):189–197. doi:10.1186/s13643-024-02461-z
14. Aygun B, Ware RE. Hydroxyurea treatment in sickle cell disease. *Expert Opin Pharmacother.* **2019**;12(7):1007–1016.
15. Alan PJ, Rashid S, Ali B. Renal protective effects of hydroxyurea in adult sickle cell disease patients: a retrospective study. *J Sickle Cell Dis.* **2024**;1(Supplement 1):yoae002.014–020. doi:10.1093/jscdis/yoae002.014
16. Han W, Zeng Z, Yang W. Effects of hydroxyurea on kidney function in sickle cell disease patients: a longitudinal cohort study. *Blood.* **2020**;136(Supplement 1):21–25. doi:10.1182/blood-2020-138753
17. Noura A, El-Sherif R, Ahmed D. Circulating endothelial cells and endothelial dysfunction in sickle cell disease patients: a marker of vascular injury. *Hematol Rep.* **2023**;15(2):85–93.
18. Solovey A, Lin Y, Browne P, Choong S, Wayner E, Hebbel RP. Circulating activated endothelial cells in sickle cell anemia. *N Engl J Med.* **2019**;333(13):1639–1644.
19. Mikhail M, Berman J, Patel R. Mechanisms underlying hydroxyurea's effect on vascular health in sickle cell disease. *J Hematol Clin Med.* **2023**;2(3):144–153.

## International Journal of General Medicine

### Publish your work in this journal

The International Journal of General Medicine is an international, peer-reviewed open-access journal that focuses on general and internal medicine, pathogenesis, epidemiology, diagnosis, monitoring and treatment protocols. The journal is characterized by the rapid reporting of reviews, original research and clinical studies across all disease areas. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-general-medicine-journal>

**Dovepress**  
Taylor & Francis Group