

Original article

Glucose-6-Phosphate Dehydrogenase Deficiency: Clinical Presentation and the Relation between Gender and the Severity of the Disease at Benghazi Children's Hospital

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Keywords.

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzyme disorder that can cause acute haemolytic anaemia following exposure to oxidative stressors. Clinical manifestations vary depending on enzyme activity and exposure to precipitating factors. This study aims to identify the most common clinical manifestations and precipitating factors of G6PD deficiency and investigate the relationship between gender and disease severity. A prospective study was conducted among 51 children aged nine years or younger attending the Haematology Clinic at Benghazi Children's Hospital between January 2019 and December 2021. G6PD deficiency was confirmed using a quantitative screening test. Clinical manifestations, precipitating factors, haemoglobin, bilirubin, and G6PD enzyme levels were assessed. Disease severity was evaluated according to haemoglobin levels, and associations with gender were analysed statistically. Of the 51 children, 44 (86.3%) were males, and seven (13.7%) were females, with a male-to-female ratio of 6.3:1. The majority of children (56.9%) experienced their first attack between two and four years of age. A positive family history was reported in 43.1%. The most common clinical manifestations were jaundice (90.2%), dark urine (80.4%), and pallor (78.4%). Fava bean consumption was the leading precipitating factor (76.5%), followed by infection (27.4%). All patients were anaemic, with 76.5% having severe anaemia (haemoglobin <7 g/dL). Elevated bilirubin levels were observed in 92.2% of patients. Most patients were classified as Class III (62.7%), followed by Class II (25.5%) and Class I (11.8%). No statistically significant associations were found between gender and haemoglobin levels ($p=0.282$), bilirubin levels ($p=0.670$), G6PD enzyme levels ($p=0.446$), or time to symptom onset ($p=0.150$). In conclusion, G6PD deficiency predominantly affected males in this study, with fava bean consumption being the most common precipitating factor. Although severe anaemia and jaundice were frequent, no statistically significant relationship was observed between gender and the measured indicators of disease severity. These findings highlight the importance of early diagnosis, family education, and avoidance of recognised oxidative triggers.

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common inherited enzymatic disorders worldwide, affecting an estimated 400 million people. Its prevalence is particularly high among populations of African, Asian, and Mediterranean ancestry, although migration has contributed to its distribution in other regions, including North and South America and parts of Northern Europe [1–3]. G6PD deficiency is clinically important because it can cause acute hemolytic anaemia following exposure to oxidative stressors. Fava bean consumption remains one of the major recognised triggers of hemolysis, particularly in Mediterranean and Middle Eastern populations, where fava beans are an important dietary component [1,3]. G6PD is an enzyme that catalyses the first step of the pentose phosphate pathway, generating nicotinamide adenine dinucleotide phosphate in its reduced form (NADPH). In red blood cells, NADPH is essential for maintaining the reduced state of glutathione and protecting cells against oxidative damage. Reduced G6PD activity compromises this protective mechanism, making erythrocytes vulnerable to oxidative stress and subsequent hemolysis [4,8]. The G6PD gene is located on the long arm of the X chromosome at Xq28.

Consequently, G6PD deficiency follows an X-linked pattern of inheritance and occurs more frequently in males, who possess only one copy of the gene. Females may be homozygous or heterozygous for G6PD variants, with clinical manifestations varying according to the proportion of erythrocytes expressing the deficient enzyme [4,6,8]. Due to random X-chromosome inactivation, heterozygous females may have a variable proportion of G6PD-deficient red blood cells and can experience clinically significant hemolysis under oxidative stress. Therefore, although the condition is often described as X-linked recessive, heterozygous females are not necessarily asymptomatic [4,8]. More than 400 G6PD variants have been described, primarily resulting from mutations in the gene's coding region that lead to amino acid substitutions and varying degrees of enzyme activity. These variants contribute to the considerable heterogeneity in clinical presentation and disease severity among affected individuals [1,4,6,8,9]. Clinical manifestations range from asymptomatic enzyme

deficiency to acute hemolytic episodes characterised by jaundice, dark-coloured urine, pallor, and anaemia. The severity of hemolysis depends on several factors, including residual enzyme activity, the nature and intensity of oxidative exposure, and individual characteristics [4,8]. Despite the recognised importance of G6PD deficiency, documenting its clinical manifestations and examining potential differences in disease severity between males and females remain important for improving clinical recognition and patient education. Understanding these characteristics may help guide preventive measures, particularly the avoidance of known precipitating factors and the early recognition of hemolytic episodes. This study aimed to identify the most common signs and symptoms of G6PD deficiency among children attending Benghazi Children's Hospital and to investigate the relationship between gender and disease severity, particularly in relation to haemoglobin and bilirubin levels and G6PD enzyme activity.

Methods

Study Design and Setting

A prospective, cross-sectional observational study was conducted among 51 children diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency who attended the Haematology Clinic at Benghazi Children's Hospital, Libya, between January 2019 and December 2021. The study population comprised 44 males and 7 females.

Data Collection

Data were collected using a structured questionnaire completed manually. Information was obtained from patients' medical records and interviews with their parents or guardians. The collected data included demographic characteristics, clinical signs and symptoms at admission, precipitating factors for acute hemolysis, and family history of G6PD deficiency. Potential precipitating factors investigated included fava bean consumption, infections, medications, and other reported exposures. Laboratory investigations performed at admission included a complete blood count, haemoglobin measurement, total serum bilirubin, and quantitative G6PD enzyme activity. G6PD activity was expressed in units per 10^{12} red blood cells ($U/10^{12}$ RBCs).

Inclusion Criteria

Children aged nine years or younger who presented with an episode of hemolysis and had G6PD deficiency confirmed by an enzyme assay were included. Both children experiencing their first hemolytic episode and those with a previously established diagnosis of G6PD deficiency were eligible.

Exclusion Criteria

Children presenting with hemolysis without laboratory confirmation of G6PD deficiency by enzyme assay were excluded from the study.

Statistical Analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS), version 26. Descriptive statistics were used to summarise the study variables. Categorical variables were presented as frequencies and percentages, whereas continuous variables were summarised using means, standard deviations, and ranges, as appropriate. The relationship between gender and selected clinical and laboratory parameters was assessed using the independent-samples t-test, where appropriate. A p-value of less than 0.05 was considered statistically significant.

Results

The study included 51 children (44 were males and 7 were females) ≤ 9 years of age who visited hematology clinic during the study period. More than half of the children, 29(56.9%), at the first attack were aged 2-4 years, followed by more than 5 years, 12(23.5%) and 10(19.6%) less than 1 year. The mean age of patients who had G6PD deficiency was 3.45 ± 2.19 , ranging from 6 months to 9 years. The percentage of males (86.3%) found to have G6PD deficiency was more than that of females (13.7%), with males to female's ratio of 6.3:1. Only one child was from Egypt; the other was Libyan. Only one child was of Egyptian nationality, while the remaining children were Libyan. Among the studied sample, 22(43.1%) of patients had a positive family history for G6PD deficiency (Table 1).

Table 1. Demographic profile of the children who suffered from G6PD deficiency

Variables	No	%
Age (Years)		
< 1	10	19.6
2-4	29	56.9
> 5	12	23.5
Sex		

Male	44	86.3
Female	7	13.7
Nationality		
Libyan	50	98.0
Egyptian	1	2.0
Family history		
Yes	22	43.1
No	29	56.9

All patients with G6PD deficiency had more than one symptom. The most prevalent signs and symptoms in G6PD-deficient patients were jaundice (90.2%), change in urine colour (80.4%), pallor (78.4%), fever (33.3%), vomiting (19.6%), abdominal pain (7.4%), diarrhoea (5.8%), headache (1.9%), and lethargy (1.9%) (Table 2).

Table 2. Signs and symptoms presented in glucose-6-phosphate dehydrogenase-deficient patients

Symptoms	No	%
Jaundice	46	90.2
Change in urine colour	41	80.4
Pallor	40	78.4
Fever	17	33.3
Vomiting	10	19.6
Abdominal pain	4	7.4
Diarrhea	3	5.8
Headache	1	1.9
Lethargy	1	1.9

Many precipitating factors such as infections, ingestion of certain drugs, and diseases can lead to hemolysis in patients with G6PD deficiency. Fava bean consumption was the most frequently reported precipitating factor, accounting for 39 cases (76.5%). Upper respiratory tract (URT) infection was reported in 7 cases (13.7%), followed by urinary tract (UT) infection in 5 cases (9.8%). Acute gastroenteritis was the least frequently reported factor, occurring in 2 cases (3.9%) (Table 3).

Table 3. Precipitating factors for hemolysis among samples studied

Precipitating factor	No	%
Fava beans	39	76.5
URT infection	7	13.7
UT infection	5	9.8
Acute gastroenteritis	2	3.9

The mean value for haemoglobin was 5.92 ± 1.92 , ranging from 2.70 to 10.0g/dl. The mean bilirubin was 4.82 ± 3.44 , ranging from 0.40 to 16mg/dl, and the mean G6PD enzyme level was 80.35 ± 63.46 , ranging from 0.40 to 215 U/10¹² RBCs (Table 4).

Table 4. Mean values for haematological and biochemical parameters

Variables	Minimum	Maximum	Mean $\pm$ SD
Level of Hb	2.70	10.0	5.92 ± 1.92
Bilirubin	0.40	16.0	4.82 ± 3.44
Level of G6PD enzyme	0.40	215.0	80.35 ± 63.46

G6PD level was measured in 51 patients and found to be low in all patients (100%). The bilirubin was high among 47(92.2%) patients and normal in 4(7.8%) patients. However, all patients were anaemic 51 (100%) (Table 5).

Table 5. Status of haematological and biochemical parameters

Variables	Normal No (%)	Abnormal No (%)
Level of G6PD enzyme	0(0.0)	51(100)
Bilirubin	4(7.8)	47(92.2)
Hemoglobin	0(0.0)	51(100)

More interestingly, serum bilirubin increased in G6PD deficiency among males more than females. The bilirubin was high among 47(92.2%) patients; of the total number of males, 95.4% had a high bilirubin level, and of the total number of females, 71.4% had a high bilirubin level (Table 6).

Table 6. Status of Bilirubin and gender

Variables	Normal		Abnormal	
	Male No (%)	Female No (%)	Male No (%)	Female No (%)
Bilirubin	2(50.0)	2(50.0)	(89.4)42	5(10.6)
Bilirubin level among males	2(4.5%)	0(0.0)	42(95.4%)	0(0.0)
Bilirubin level among females	0(0.0)	2(28.5)	0(0.0)	5(71.4%)

Of the whole studied sample, (76.5%) were found to have severe anaemia (Hb level less than 7gm/dl), while only (23.5%) of the patients had moderate anaemia (Hb level 7-10 gm/dl) (Table 7).

Table 7. Status of anaemia among glucose-6-phosphate dehydrogenase-deficient patients

Variables	No	%
Severe anaemia (Hb <7 g/dL)	39	76.5
Moderate anaemia (Hb 7–10 g/dL)	12	23.5

The mean blood haemoglobin level of the female patients was 6.65 ± 2.52 , and the mean blood haemoglobin level of males was 5.8 ± 1.8 . However, there was no statistically significant difference between gender and Hb level ($P=0.0282$). The mean bilirubin level of the female patients was 5.2 ± 4.2 , and the mean bilirubin level of males was 4.76 ± 3.35 . However, there was no statistically significant difference between gender and bilirubin level ($P=0.0670$). The mean level of G6PD enzyme of the female patients was 97.54 ± 61.40 , and the mean level of G6PD enzyme of males was 77.6 ± 64.03 . However, there was no statistically significant difference between gender and level of G6PD enzyme ($P=0.0446$) (Table 8).

Table 8. Comparison of haematological and biochemical parameters by gender

Variables	Gender		t-test	P-value
	Male Mean $\pm$ SD	Female Mean $\pm$ SD		
Haemoglobin	5.8 ± 1.8	6.65 ± 2.52	-1.089	0.282
Bilirubin	4.76 ± 3.35	5.2 ± 4.2	-0.31	0.670
Level of G6PD enzyme	77.6 ± 64.03	97.54 ± 61.40	-0.769	0.446

The mean time of symptoms after exposure to the precipitating factor was 34.53 ± 28.22 , ranging from 3 to 120 hrs. The mean time of symptoms after exposure to the precipitating factor among males was 32.25 ± 28.16 , and the mean time of symptoms after exposure to the precipitating factor among females was 48.86 ± 26.02 . However, there was no statistically significant difference between gender and time of symptoms after exposure to the precipitating factor ($P=0.0150$) (Table 9). Most of patients were in class 3(62.7%) follow by 13(25.5%) in class 2 and 6(11.8%) in class 1 (Table 10).

Table 9. Comparison of Time of symptoms in hours after exposure to the precipitating factor and gender

Time of symptoms in hrs after exposure to precipitating factor	Gender		t-test	P-value
	Male Mean $\pm$ SD	Female Mean $\pm$ SD		
	32.25 ± 28.16	48.86 ± 26.02	-1.46	0.150

Table 10. Classification of patients according to the WHO classification of G6PD deficiency

	Patients No (%)	G6PD level in U/10 ¹² RBCs
Class 1	6(11.8)	4.8<
Class 2	13(25.5)	4.8-48.3
Class 3	32(62.7)	48.3-290
Class 4	0(0.0)	290-412
Class 5	0(0.0)	>412

Discussion

This prospective, cross-sectional observational study investigated the clinical presentation of glucose-6-phosphate dehydrogenase (G6PD) deficiency and the relationship between gender and disease severity among children attending the Haematology Clinic at Benghazi Children's Hospital between January 2019 and December 2021. A total of 51 children were included, comprising 44 males (86.3%) and seven females (13.7%). The findings provide information on the common clinical manifestations, precipitating factors, laboratory characteristics, and potential gender differences in the severity of G6PD deficiency. Regarding age distribution, more than half of the children (56.9%) experienced their first hemolytic episode between two and four years of age, while 19.6% were younger than one year. The mean age was 3.45 ± 2.19 years, with an age range of six months to nine years. These findings are broadly consistent with previous studies reporting that clinically significant hemolytic episodes frequently occur during early childhood [10,11,16,20,21,24]. However, Laosombat et al. reported a different age distribution, with approximately half of the affected children younger than two years and the remainder predominantly between two and five years [26]. The relatively lower frequency of recognised attacks at older ages in the present study may partly reflect increased awareness among families and the avoidance of known precipitating factors following an initial episode. This interpretation is consistent with reports suggesting that neonatal screening and health education can reduce the occurrence of favism [28]. Nevertheless, the present study cannot establish an age-related decline in disease prevalence because it included children presenting to a single haematology clinic rather than a population-based sample. Males accounted for 86.3% of the study population, compared with 13.7% of females, yielding a male-to-female ratio of 6.3:1. This predominance is consistent with findings from previous studies of G6PD deficiency and favism [10,12,15–17,20–22,26]. The difference is biologically plausible because the G6PD gene is located on the X chromosome. Males have only one copy of this gene and may express deficiency when that copy carries a pathogenic variant.

In contrast, females may be homozygous or heterozygous for G6PD variants, and the clinical expression of deficiency among heterozygous females can vary according to X-chromosome inactivation [13,14]. However, the male predominance observed in this study should not be interpreted as evidence that females are protected against clinically significant hemolysis, particularly because the study included relatively few female patients. Fava bean consumption was the most frequently reported precipitating factor, accounting for 76.5% of hemolytic episodes. This finding agrees with several previous studies in which fava bean ingestion was identified as an important trigger of acute hemolysis among G6PD-deficient children [16–18,22,26]. In some of these studies, fava bean consumption was reported in all affected patients [16–18,22]. Differences in the reported proportions may reflect variations in dietary practices, geographical location, patient selection, family awareness, and the relative contribution of other oxidative triggers.

Fava beans contain compounds, including vicine and convicine, that can generate oxidative stress and precipitate hemolysis in susceptible individuals. Given the importance of fava beans in the diet of many Mediterranean and Middle Eastern populations, educating families about the association between their consumption and hemolytic episodes remains an important preventive measure. Infections were the second most frequently reported precipitating factor, occurring in 27.4% of patients. Upper respiratory tract infections accounted for 13.7%, urinary tract infections for 9.8%, and acute gastroenteritis for 3.9%. These findings support the recognised role of infections in precipitating hemolytic episodes among individuals with G6PD deficiency. Hagag et al. also identified infections, including tonsillitis and urinary tract infections, among the reported triggers of hemolysis in Egyptian children [10].

In contrast, a study conducted by Al-Azzam et al. identified drugs as the second most common precipitating factor after the principal trigger, followed by upper respiratory tract infections [19]. In the present study, drug exposure was infrequently reported. One patient developed a hemolytic episode following ingestion of a large quantity of blue food dye. This isolated observation should be interpreted cautiously, as the specific substance and its potential oxidative properties were not established. Overall, the findings highlight the importance of identifying potential triggers through a detailed clinical history. The most prevalent clinical manifestations were jaundice (90.2%), dark-coloured urine (80.4%), and pallor (78.4%). These findings are consistent with the clinical presentation of acute hemolysis, in which red blood cell destruction produces anaemia/anaemia, increased bilirubin concentrations, and haemoglobinuria. Nevertheless, differences in the predominant manifestations have been reported across studies. Alavi et al. identified dark urine as the most common presenting feature, followed by pallor and jaundice [22]. Other studies reported pallor as the leading clinical manifestation [17,22,27], whereas several investigations documented the frequent coexistence of jaundice, pallor, and changes in urine colour [16,24,26]. Such differences may reflect the timing of presentation, the severity of hemolysis, the criteria used to define symptoms, and differences in the populations studied. The high frequency of these manifestations in the present study emphasises their clinical importance in recognising acute hemolytic episodes among children with suspected G6PD deficiency. All patients in the present study were anaemic at admission. Haemoglobin concentrations ranged from 2.7 to 10.0 g/dL, with a mean of 5.92 ± 1.92 g/dL.

Severe anaemia, defined as a haemoglobin concentration below 7 g/dL, occurred in 76.5% of patients, while 23.5% had moderate anaemia, with haemoglobin concentrations between 7 and 10 g/dL. These findings indicate that substantial anaemia was common among the children presenting to this clinic. Similar reductions in haemoglobin levels have been described in previous studies of children presenting with favism and acute hemolysis [16,24,26]. However, the proportion

of patients with severe anaemia differed from that reported by Al-Azzam et al., who found severe anaemia in 50% of patients, moderate anaemia in 46.5%, and mild anaemia in 2.3% [19]. Differences in clinical severity, referral patterns, the timing of presentation, and the definitions used to classify anaemia may account for some of this variation. The mean haemoglobin concentration was 6.65 ± 2.52 g/dL among females and 5.80 ± 1.80 g/dL among males. Although the mean was numerically higher among females, the difference was not statistically significant ($p = 0.282$). Therefore, the present study did not demonstrate a statistically significant association between gender and haemoglobin concentration. Bancone et al. discussed sex-related differences in anaemia among individuals with G6PD deficiency, emphasising that clinical and haematological manifestations may vary between males and females [27]. However, direct comparison with the present findings is limited by differences in study populations and outcome definitions. In addition, the small number of females in our sample limits the precision and statistical power of gender comparisons.

Consequently, the absence of statistical significance should not be interpreted as definitive evidence that disease severity is equivalent between genders. Elevated serum bilirubin concentrations were observed in 92.2% of patients, with values ranging from 0.4 to 16.0 mg/dL and a mean of 4.82 ± 3.44 mg/dL. This finding is consistent with the high frequency of jaundice and supports the presence of increased bilirubin production associated with hemolysis. Previous studies have also reported elevated bilirubin concentrations among children presenting with G6PD-related hemolytic episodes [10,24]. In the present study, elevated bilirubin was reported in 95.4% of males and 71.4% of females. Despite this numerical difference, no statistically significant association was observed between gender and bilirubin levels ($p = 0.670$). Meloni et al. reported sex-related differences in bilirubin concentrations among G6PD-deficient individuals with favism, although their findings cannot be directly compared with the present study without considering differences in patient characteristics and bilirubin measurements [13]. Given the small female sample, further studies involving larger and more balanced groups are required to determine whether meaningful gender differences exist. Quantitative G6PD enzyme activity was assessed, and all included patients were classified as deficient according to the study's diagnostic criteria. Most patients were classified as Class III (62.7%), followed by Class II (25.5%) and Class I (11.8%). This distribution is broadly consistent with the findings of Mohamed Bazina and Gheriani, who reported a predominance of Class III deficiency in their study of patients presenting with favism [16]. Al-Azzam et al. also reported reduced G6PD activity among most patients included in their study [19]. However, comparisons between enzyme classifications should be made cautiously because classification systems, assay methods, and thresholds may differ between studies. The mean G6PD enzyme activity was 97.54 ± 61.40 U/ 10^{12} RBCs among females and 77.60 ± 64.03 U/ 10^{12} RBCs among males. The difference was not statistically significant ($p = 0.446$). This finding differs from the sex-related variation in enzyme activity reported by Meloni et al. [13]. Nevertheless, the small number of female participants limits the ability to identify gender-related differences. Furthermore, enzyme activity in heterozygous females can vary substantially because of X-chromosome inactivation. Quantitative enzyme activity should therefore be interpreted in conjunction with the assay method, reference intervals, and clinical context. A positive family history of G6PD deficiency was reported in 43.1% of patients, while 56.9% had no reported family history. These findings are consistent with studies documenting familial occurrence of G6PD deficiency [14,16]. However, Hagag et al. reported a higher proportion of patients with a positive family history, at 63.6% [10].

Differences in family awareness, previous testing, access to diagnostic services, and the accuracy of information obtained from parents may explain some of this variation. The absence of a reported family history does not exclude an inherited disorder, particularly when relatives have not previously been tested or have remained asymptomatic. Finally, the interval between exposure to a suspected precipitating factor and the appearance of symptoms ranged from 3 to 120 hours, with a mean of 34.53 ± 28.22 hours. No statistically significant association was found between gender and the interval to symptom onset ($p = 0.150$). These findings are broadly consistent with the clinical observations reported by Hagag et al. [10]. Other studies, including those by Mohamed Bazina and Gheriani and Nourz et al., reported intervals commonly ranging from 24 to 72 hours [16,24]. The wider range observed in the present study may reflect differences in the type and intensity of exposure, the timing of symptom recognition, and the accuracy of parental recall. Overall, the findings demonstrate that fava bean consumption was the leading reported precipitating factor, while jaundice, dark urine, pallor, and severe anaemia were prominent clinical features. Although males constituted the majority of patients, no statistically significant associations were identified between gender and haemoglobin concentration, bilirubin level, G6PD enzyme activity, or time to symptom onset. These results should be interpreted in light of the small sample size, particularly the limited number of female participants, and the single-centre study setting.

Conclusion

G6PD deficiency predominantly affected males among children attending Benghazi Children's Hospital during the study period. Fava bean consumption was the most frequently reported precipitating factor for hemolytic episodes, followed by infections. Jaundice, dark-coloured urine, and pallor were the most common clinical manifestations, and all patients presented with anaemia, with most experiencing severe anaemia. No statistically significant associations were identified between gender and haemoglobin concentration, bilirubin level, G6PD enzyme activity, or the interval between exposure and symptom onset. However, the small number of female participants limits the strength of these conclusions. Larger

studies involving more balanced gender representation are needed to clarify potential differences in clinical presentation and disease severity.

Recommendations

1. Consider neonatal G6PD screening, particularly in settings where the condition is prevalent and in families with a known history of G6PD deficiency, in accordance with local screening policies and clinical guidelines.
2. Provide parents and caregivers with clear information about recognised oxidative triggers, particularly fava beans, and the importance of seeking prompt medical assessment when symptoms of hemolysis occur.
3. Encourage early assessment and appropriate management of infections, which may precipitate hemolytic episodes in susceptible children.
4. Educate families and healthcare professionals about medications and other substances that may trigger hemolysis in G6PD-deficient individuals. Suspected exposures should be evaluated according to established clinical guidance.
5. Conduct multicenter studies with larger sample sizes and adequate representation of females to investigate potential gender-related differences in clinical manifestations, enzyme activity, and disease severity. Genetic analysis may also help characterise G6PD variants and explore their relationship with clinical outcomes.

Study Limitations

This study has several limitations. First, it was conducted at a single pediatric hospital, and the findings may not represent all children with G6PD deficiency in Benghazi or other regions of Libya. Second, the sample size was relatively small, particularly among females, limiting the statistical power to detect gender-related differences. Third, children diagnosed with G6PD deficiency who did not attend or follow up at the haematology clinic were not included, potentially introducing selection bias. Fourth, the limited availability of comparable studies specifically investigating the relationship between gender and disease severity restricted direct comparisons with previous research. Finally, information regarding precipitating factors and the interval between exposure and symptom onset was partly obtained from parents or medical records and may have been affected by recall or documentation bias.

Conflict of interest. Nil

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