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Original article

Impact of G6PD deficiency on liver damage and disease progression in hepatocellular carcinoma: a cross-sectional study in Thailand

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Abstract

Background: Glucose 6-phosphate dehydrogenase (G6PD) is a key enzyme involved in the pentose phosphate pathway that produces reduced nicotinamide adenine dinucleotide phosphate to support redox homeostasis and cancer cell proliferation. While G6PD deficiency has been linked to reduced cancer risk, its influence on hepatocellular carcinoma (HCC) remains unclear.
Objectives: This study aimed to investigate the prevalence of G6PD deficiency in patients with HCC and its association with clinical parameters across the disease stages.
Methods: A cross-sectional study analyzed G6PD activity and clinical data from 174 patients with HCC, 100 patients infected with the hepatitis B virus (HBV), and 154 healthy controls. Peripheral blood G6PD activity was measured, and the clinical parameters were compared between patients with early- and advanced-stage HCC with and without G6PD deficiency.
Results: The prevalence of G6PD deficiency was comparable across patients with HCC (6.9%), patients with HBV infection (6.0%), and healthy controls (6.5%) ($P = 0.97$), with no notable difference in clinical parameters between early- (6.7%) and advanced-stage HCC (7.0%). Median G6PD activity was significantly higher in patients with HCC (7.9 ± 2.1 U/g Hb) compared to healthy controls (7.1 ± 2.5 U/g Hb) ($P < 0.05$). Patients with advanced-stage HCC exhibited elevated G6PD activity (8.1 ± 2.5 U/g Hb), largely because of anemia. The patients with G6PD deficiency and HCC, particularly at the advanced stage, had elevated liver damage markers, including alkaline phosphatase (125.0 ± 68.8 U/L), serum glutamic-oxaloacetic transaminase (69.5 ± 78.0 U/L), and alpha-fetoprotein (258.8 ± 1,010.1 ng/mL) levels.
Conclusion: G6PD deficiency does not appear to reduce HCC susceptibility but is associated with increased liver damage in patients with HCC at an advanced stage. These findings highlight the potential importance of G6PD in the progression of liver cancer and the need for further research regarding its therapeutic implications.

Keywords: G6PD deficiency; HCC; hepatocellular carcinoma; liver damage; peripheral blood G6PD activity.

Cancer cells undergo metabolic reprogramming to support their rapid proliferation, a hallmark of tumorigenesis.[1] One key adaptation is the Warburg effect, where cancer cells preferentially utilize glycolysis over oxidative phosphorylation, even under normoxic conditions.[2] This shift enhances glucose uptake and generates intermediates that are necessary for biosynthesis and survival. The pentose phosphate pathway (PPP) is driven by glucose 6-phosphate dehydrogenase (G6PD) (E.C.1.1.1.49) and plays a

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crucial role in this metabolic reprogramming by producing nicotinamide adenine dinucleotide phosphate (NADPH) for lipid synthesis and ribose 5-phosphate (R5P) for nucleotide synthesis. Furthermore, NADPH helps to generate reduced glutathione (GSH), which protects cells from oxidative stress caused by reactive oxygen species.[3,4] G6PD activity, particularly in the context of cell cycle progression, facilitates biosynthesis and the metabolic demands of rapidly proliferating tumor cells.[3,5,6]

Elevated expression levels of G6PD have been consistently reported in various malignancies, including hepatocellular carcinoma (HCC), where it is linked to a poor prognosis and increased tumor aggressiveness.[7-15] Despite its essential role in tumor progression, G6PD deficiency, which is a hereditary enzyme defect that affects approximately 400 million individuals worldwide, particularly in Africa, the Mediterranean, the Middle East, and Southeast Asia[16,17], is proposed to be linked to reduced tumorigenesis by impairing the PPP, thereby leading to a shortage of NADPH and R5P, which is crucial for the survival of cancer cells. G6PD deficiency prevalence varies across regions, with higher frequencies observed in Southeast Asia, including Laos, Cambodia, Thailand, and Myanmar. [18] Although establishing a low cancer prevalence in G6PD-deficient populations is challenging because of variations in genetic defect frequency, restricted ethnic distribution, and cancer tissue specificity[19,20], recent findings have indicated the reduced susceptibility to colorectal cancer and HCC in individuals with G6PD deficiency.[21] HCC is a major cause of cancer-related mortality worldwide that is often only diagnosed at advanced stages with limited treatment options. Despite previous studies focusing on the prevalence of G6PD deficiency and its impact on patients with cancer[21,22], the clinical implications of G6PD deficiency in HCC, particularly its association with liver damage and disease progression, remain poorly understood.

The study aimed to investigate the prevalence of G6PD deficiency in patients with HCC and its association with the clinical parameters across different disease stages. By elucidating the role of G6PD deficiency in HCC progression and liver damage, our findings provide insights into the potential therapeutic application of targeting G6PD in liver cancer management.

Materials and methods

This study was reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no. 806/61, COA no. 218/2019; IRB no. 803/2017, COA no. 803/2017) and the Research Ethics Committee of the National Blood Centre, Thai Red Cross Society (COA no. NBC 7/2016). The protocol of this study was conducted in accordance with the Declaration of Helsinki for the participation of human individuals. Written informed consent was obtained from each participant before they underwent any study procedures.

Patient specimens

In this cross-sectional study, 274 patients were randomly enrolled, including 100 individuals with hepatitis B virus (HBV) infection but not HCC and 174 individuals with HCC (95 non-HBV-related HCC and 79 HBV-related HCC). HCC diagnosis was confirmed through clinical criteria, imaging (ultrasound, CT, and MRI), and biomarkers, with serum alpha-fetoprotein (AFP) as a supporting marker. HBV infection was confirmed by serological testing for HBsAg and HBV-DNA quantification, thereby ensuring the accurate classification of HCC and HBV status. [23] Participants were recruited in 2019 from King Chulalongkorn Memorial Hospital, Thai Red cross Society, Bangkok, Thailand. In addition, 154 healthy volunteers were randomly selected from blood donors affiliated with the Thai Red Cross Society in Bangkok, Thailand. Among the 174 patients with HCC, stratification based on the Barcelona Clinic Liver Cancer stages revealed 60 cases in the early stages (0, A) and 114 cases in the advanced stages (B, C, and D) (**Figure 1**). Fifty-eight (73.4%) of the 79 patients with HBV-related HCC were in the advanced stages. Blood samples were collected at a single time point prior to any medical treatment to prevent the confounding effects of chemotherapy on the liver enzymes and G6PD activity. Clinical data were gathered at the time of initial diagnosis and tracked until recurrence, death, or the last follow-up visit to establish the prognosis.

Measurement of peripheral blood G6PD activity

G6PD activity in peripheral blood samples was assessed using the Trinity Biotech quantitative G6PD assay (Trinity Biotech, Ireland). The G6PD activity levels, indicated by NADPH generation, were

determined by measuring the change in absorbance at 340 nm over a 5-min period at 37°C using a temperature-regulated spectrophotometer (Shimadzu UV-1800; Shimadzu, Japan). Hemoglobin concentration, which is necessary for calculating G6PD activity (U/g Hb), was determined with a hemoglobin photometer (Hemocue, Ängelholm, Sweden). Participants with G6PD activity below 2.2 U/g Hb (<30.0% of the normal median)[24] were defined as having G6PD deficiency.

Statistical analysis

All statistical analyses were performed using SPSS version 29 (IBM SPSS software, IL, USA). The data distribution was assessed using the Kolmogorov–Smirnov/Shapiro–Wilk tests. Parametric tests were performed on normally distributed data, which were presented as percentages and the mean ± standard deviation(SD). Nonparametric tests were used for data that were not normally distributed and were presented as the median ± interquartile range (IQR). Categorical variables were analyzed using Pearson's $\chi 2$ test or Fisher's Exact test, while the quantitative variables were assessed using either the Mann–Whitney U test, Student's *t*-test, or Kruskal–Wallis one-way analysis of variance. A statistically significant difference was defined as a two-sided $P < 0.05$.

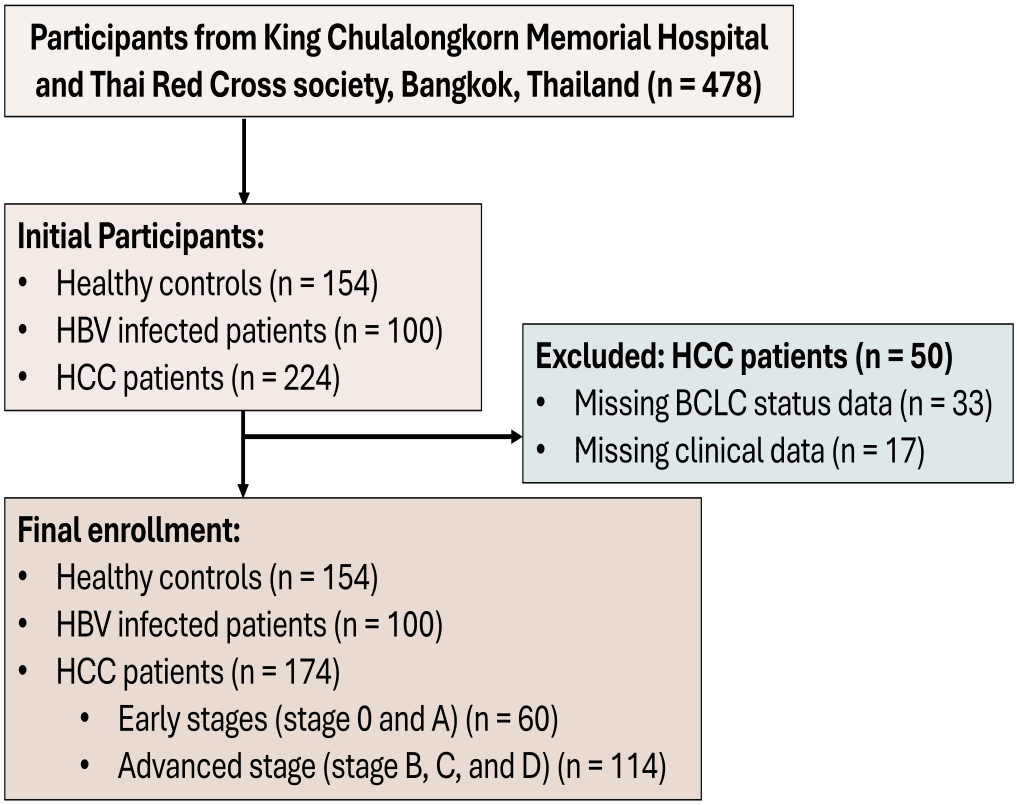

Figure 1. Flow diagram for patient enrollment.

Results

Demographic data and prevalence of G6PD deficiency

The majority of participants in the study were males, with a higher proportion among patients with HCC compared to that of patients with HBV infection and the healthy controls ($P < 0.001$) (**Table 1**). Patients with HCC were significantly older than patients with HBV infection and the healthy controls ($P < 0.001$). The prevalence of G6PD deficiency was comparable across the three groups: healthy controls, patients with HBV infection, and patients with HCC ($P = 0.965$). No significant difference was observed for G6PD deficiency prevalence between the early and advanced stages of HCC ($P = 1.000$).

Peripheral blood G6PD activity

The median peripheral blood G6PD activity in patients with HCC was significantly higher than that in the healthy controls ($P = 0.048$) and patients with HBV infection ($P = 0.035$) (**Table 1**). Patients with advanced-stage HCC exhibited the highest G6PD activity, significantly exceeding that of patients with early-stage HCC ($P = 0.006$) (**Table 1**). Although age and gender differed significantly among the patient groups, neither had a significant impact on the peripheral blood G6PD activity (age: $P = 0.115$; gender: $P = 0.934$). This elevation in G6PD activity was primarily attributed to anemia in patients with advanced-stage HCC, as reduced hemoglobin levels (**Table 2**) are commonly used to normalize G6PD measurements.

Association of G6PD deficiency with clinical parameters in patients with HCC

In patients with advanced-stage HCC and normal G6PD levels, significant reductions in hemoglobin ($P = 0.004$) and hematocrit levels ($P = 0.005$) were observed compared to those of patients with early-stage HCC. In addition, patients with advanced-stage HCC and normal G6PD levels had significantly higher platelet counts ($P < 0.001$) and levels of alkaline phosphatase (ALP) ($P < 0.001$), serum glutamic-oxaloacetic transaminase (SGOT) ($P = 0.001$), serum glutamate-pyruvate transaminase (SGPT) ($P = 0.006$), and AFP ($P < 0.001$) compared to those of patients with early-stage HCC. Among patients with HCC and G6PD deficiency, advanced-stage individuals exhibited anemia and elevated levels of ALP, SGOT, and AFP, which were above the normal reference ranges. However, these parameters were not significantly different compared to those of patients with advanced-stage HCC and normal G6PD activity (**Table 2**).

Table 1. Demographic data and prevalence of G6PD deficiency among study participants.

Parameter	Healthy (n = 154)	HBV-infected HCC (n = 100)	HCC (n=174)	*P*-value	HCC		*P*-value
					Early-stage (n = 60)	Advanced-stage (n = 114)	
Gender (males) (%)	99 (64.3)†	51# (51.0)†	138 (79.3)†	< 0.001†	48 (80.0)	90 (78.9)	0.895
Age (years) (mean ± SD)	55.1 ± 12.6 (22.0 - 84.0)	39.4 ± 11.6 (21.0 - 66.0)	62.5 ± 11.6 (23.0 - 89.0)	< 0.001$	63.8 ± 11.0 (23.0 - 84.0)	61.0 ± 11.8 (33.0 - 89.0)	0.237$$
G6PD deficiency (%)	10 (6.5)	6 (6.0)	12 (6.9)	0.965†	4 (6.7)	8 (7.0)	1.000*
Male (%)	7/99 (7.1)	6/51# (11.8)	11/138 (8.0)	0.677†	4/48 (8.3)	7/90 (7.8)	1.000*
Female (%)	3/55 (5.5)	0/46# (0.0)	1/36 (2.8)	0.419†	0/12	1/24 (4.2)	1.000*
G6PD activity (median ± IQR)	7.1 ± 2.5 (0.1 - 14.3)	7.2 ± 1.9 (0.5 - 25.5)	7.9 ± 2.1 (0.2 - 21.9)	0.009††	7.4 ± 1.6 (0.2 -14.0)	8.1 ± 2.5 (0.4 - 21.9)	0.006**

There were 3 cases where gender information was not available.
† Pearson's $\chi 2$ test between healthy, HBV-infected, and HCC patients.
$ ANOVA post-hoc test (Bonferroni correction) between healthy, HBV-infected, and HCC patients.
$$ Student's t-test between early- and advanced-stage patients.
* Fisher's Exact Test between early- and advanced-stage patients.
†† Kruskal-Wallis One-Way ANOVA between healthy, HBV-infected, and HCC patients.
** Mann-Whitney U test between early- and advanced-stage patients.

Table 2. Hematological parameters and liver function among HCC patients.

Parameter	Normal range	Early-stage (n = 60)			Advanced-stage (n = 114)			*P*-value[#]	*P*-value[##]
		G6PD deficiency (n = 4)	G6PD normal (n = 56)	*P*-value[$]	G6PD deficiency (n = 8)	G6PD normal (n = 106)	*P*-value[$]		
Hb (g/dL)	13.0 - 17.0	12.1 ± 0.8* (11.1 - 12.8)	12.7 ± 1.6* (9.9 - 16.4)	0.480[†]	10.7 ± 3.8* (8.3 - 13.5)	11.8 ± 2.1* (6.2 - 18.1)	0.199[†]	0.206	**0.004**
Hct (%)	39.0 - 51.0	36.5 ± 2.2* (33.8 - 39.0)	37.8 ± 4.7* (28.0 - 48.8)	0.322[†]	32.2 ± 5.5* (25.5 - 40.1)	35.3 ± 5.9* (21.7 - 52.8)	0.154[†]	0.171	**0.005**
WBC (x10^9/L)	4.5 - 11.0	4.6 ± 1.4 (4.2 - 5.9)	5.0 ± 2.7 (2.3 - 9.6)	0.505	6.8 ± 8.6 (2.9 - 15.8)	5.8 ± 2.8 (1.5 - 15.9)	0.512	0.234	0.078
Platelet (x10^9/L)	150.0 - 450.0	134.5 ± 36.0 (92.0 - 140.0)	118.0 ± 91.0 (31.0 - 329.0)	0.767	211.0 ± 291.0 (81.0 - 402.0)	169.0 ± 130.0 (37.0 - 483.0)	0.603	0.734	**<0.001**
Bilirubin (mg/dL)	0.2 - 1.2	0.8 ± 1.1 (0.5 - 1.8)	0.7 ± 0.5 (0.3 - 2.9)	0.705	0.9 ± 1.0 (0.5 - 2.5)	0.8 ± 0.6 (0.1 - 3.7)	0.556	1.000	0.545
ALP (U/L)	40.0 - 120.0	88.5 ± 33.8 (54.0 - 96.0)	79.0 ± 62.0 (38.0 - 228.0)	0.833	125.0 ± 68.8 (80.0 - 427.0)	107.0 ± 85.5 (45.0 - 547.0)	0.483	0.089	**<0.001**
SGOT (U/L)	5.0 - 35.0	36.0 ± 78.0 (20.0 - 119.0)	47.0 ± 39.0 (15.0 - 248.0)	0.651	69.5 ± 78.0 (29.0 - 115.0)	56.5 ± 67.0 (18.0 - 573.0)	0.961	0.396	**0.001**
SGPT (U/L)	0.0 - 40.0	23.5 ± 83.0 (16.0 - 126.0)	33.5 ± 35.0 (1.0 - 276.0)	0.771	29.5 ± 78.0 (13.0 - 105.0)	43.0 ± 40.0 (11.0 - 189.0)	0.412	0.865	**0.006**
Albumin (g/dL)	3.5 - 5.0	4.0 ± 0.3* (3.8 - 4.3)	3.6 ± 0.5* (2.6 - 4.3)	0.214[†]	3.2 ± 0.2* (3.1 - 3.5)	3.3 ± 0.5* (2.1 - 4.5)	0.866[†]	**0.026**	**0.009**
Creatinine (mg/dL)	0.7 - 1.2	0.8 ± 0.2 (0.7 - 0.9)	0.9 ± 0.3 (0.5 - 3.9)	0.097	0.8 ± 0.2 (0.6 - 2.2)	0.9 ± 0.3 (0.4 - 2.6)	0.214	0.497	0.136
INR	1.0	1.2 ± 0.3 (1.0 - 1.3)	1.1 ± 0.2 (1.0 - 1.5)	0.351	1.2 ± 0.1 (0.9 - 1.3)	1.1 ± 0.2 (0.9 - 1.5)	0.305	0.734	0.390
AFP (ng/mL)	5.0 - 10.0	38.2 ± 5,801.0 (7.2 - 7,726.8)	6.4 ± 43.6 (1.6 - 4220.5)	0.083	258.8 ± 1010.1 (2.0 - 2715.0)	81.5 ± 793.7 (0.7 – 88,110.3)	0.623	0.705	**<0.001**

[$] Mann-Whitney U test between G6PD deficiency and normal.

* Mean ± SD.

[†] Student's t-test between G6PD deficiency and normal.

[#] compared between groups of patients with G6PD deficiency in early and advanced-stage.

[##] compared between groups of patients with G6PD normal in early and advanced-stage.

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; Hb, hemoglobin; Hct, hematocrit; INR, international normalized ratio; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamate-pyruvate transaminase; WBC, white blood cell.

Discussion

HCC is the predominant cause of cancer-related mortality worldwide, with most cases only diagnosed at advanced stages, which limits treatment options and contributes to poor prognosis.[25, 26] Cancer cells require increased biosynthesis and redox homeostasis to sustain their rapid proliferation. G6PD is central to meeting these demands by producing NADPH for reductive biosynthesis and protection against oxidative stress and producing R5P for nucleotide synthesis.[3, 4] While elevated G6PD expression levels have been implicated in the progression of several malignancies, including HCC, the influence of hereditary G6PD deficiency on liver cancer progression remains poorly understood.[7-15, 21, 27]

In this study, we found that G6PD deficiency was not associated with reduced HCC susceptibility, as its prevalence was comparable across the groups of patients with HCC, patients with HBV infection, and healthy controls. These findings align with the reported prevalence of G6PD deficiency in the Thai population (5.6% –11.1%)[28, 29] and suggest that G6PD deficiency may not play a protective role in HCC initiation. However, this contrasts with previous studies, which proposed reduced cancer risk in G6PD-deficient individuals, particularly regarding colorectal cancer and HCC.[21, 30] The lack of observed protective effect may reflect compensatory metabolic mechanisms, such as the activation of nucleotide salvage pathways or alternative NADPH-generating enzymes, including NADP(+)-dependent isocitrate dehydrogenase and the cytosolic malic enzyme, which may mitigate the impact of G6PD deficiency on tumor cell survival.[31-33] Further studies monitoring these compensatory pathways may provide valuable insights into their roles in sustaining cancer proliferation.

Interestingly, we observed significantly elevated peripheral blood G6PD activity in patients with advanced-stage HCC compared with that of patients with early-stage HCC and healthy controls. While this observation is consistent with reports of G6PD upregulation in advanced-stage cancers, such as Merkel cell carcinoma[34], the underlying cause in our study appears distinct. Rather than reflecting the increased enzymatic expression in tumor cells, this elevated blood G6PD activity is likely a technical artifact driven by anemia, which is a common feature in patients with advanced cancer. As G6PD activity is typically normalized to hemoglobin levels, low hemoglobin concentrations can artifactually inflate calculated G6PD values. Therefore, the apparent increase in peripheral G6PD activity in advanced-stage HCC may be, at least in part, a consequence of hemoglobin normalization rather than a true upregulation of enzymatic activity. This distinction is important when interpreting enzymatic activity in systemic samples.

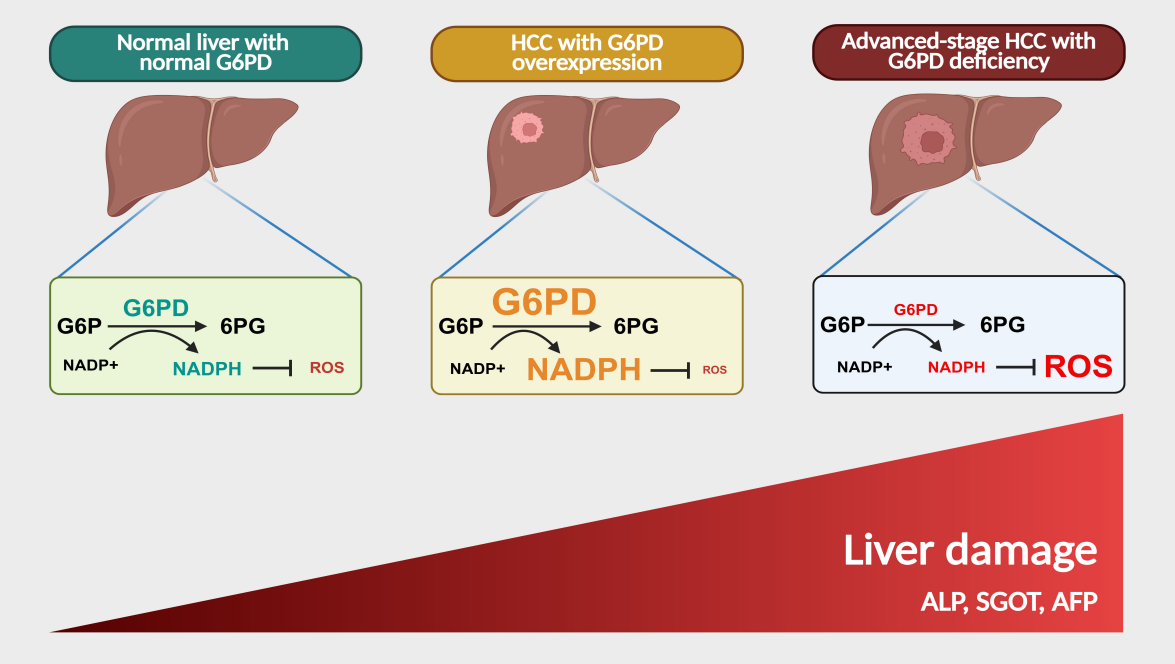

Figure 2. The proposed link between G6PD deficiency and increased liver damage in HCC, highlighting oxidative stress and metabolic vulnerability in advanced disease stage.

Despite its lack of a protective effect on cancer risk, G6PD deficiency was associated with increased liver injury in patients with advanced-stage HCC. Elevated levels of ALP, SGOT, and AFP were observed in G6PD-deficient individuals, although the differences were not significant because of the small sample size. These trends may reflect the crucial role of NADPH in hepatocyte metabolism. As the PPP is the primary source of NADPH in liver cells, particularly in the absence of mitochondrial malic enzyme activity[35] , G6PD deficiency may impair redox homeostasis, promote oxidative stress, and exacerbate liver damage.[36, 37] This association suggests that G6PD deficiency, while not reducing HCC susceptibility, may worsen the clinical outcomes in patients with advanced disease. Targeting G6PD activity and its associated pathways may present a therapeutic strategy for mitigating liver damage and improving outcomes in patients with HCC.

Our findings highlight the need to interpret peripheral G6PD activity in the context of the patient's hematological status and underscore the potential relevance of G6PD-related pathways in the progression of liver cancer. However, this study is limited by the small number of patients with HCC and G6PD deficiency, which may reduce the statistical power. Future research with larger cohorts is needed to confirm these observations and further explore the metabolic consequences of G6PD deficiency in liver cancer **(Figure 2)**.

Conclusion

This study found no significant association between G6PD deficiency and HCC susceptibility, as the prevalence thereof was similar among patients with HCC, patients with HBV infection, and healthy controls. However, patients with advanced-stage HCC exhibited elevated peripheral blood G6PD activity, which was likely influenced by anemia, but those with G6PD deficiency exhibited increased markers of liver damage. These findings suggest that although G6PD deficiency does not reduce HCC risk, it may exacerbate liver damage in advanced disease stages. Future studies should explore compensatory metabolic pathways and assess the therapeutic potential of targeting G6PD-related mechanisms in HCC.

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Conflict of interest statement

The authors declare that they have no competing interests.

Data sharing statement

All data generated or analyzed during this study are included in this published article.

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