ORIGINAL RESEARCH

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G8 Frailty Assessment Tool as a Predictor of Quality of Life in Elderly Patients Receiving Sorafenib for Hepatocellular Carcinoma. A Prospective Cohort

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Abstract

Objective: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the fourth most common in Egypt. Studies report a significant age-specific increase in HCC development. Sorafenib is frequently used to treat patients with HCC across all age groups, including the elderly. Assessing treatment tolerability, quality of life (QoL), and symptom burden in older patients is crucial because frailty is more prevalent with advancing age and can lead to poorer outcomes. The G8 has demonstrated superior prediction of complications and symptom burden among older adults with various cancers. Therefore, our primary aim is to assess G8 frailty tool as predictor of QoL in elderly patients with HCC receiving sorafenib. Our secondary aim was to assess the correlation between G8 and side effects and decompensation during sorafenib treatment.

Materials and Methods: The study subjects were elderly patients (aged 60 years or older) presenting to HCC outpatient clinics at Ain Shams University who were eligible for sorafenib. Patients were initiated on sorafenib and followed for three months. G8 was assessed before the first dose of sorafenib. European Organization for Research and Treatment of Cancer Quality of Life 15 items Questionnaire for Palliative Care scores and timed up and go test (TUGT) were assessed before the first dose and repeated after one and three months of treatment. Data were tabulated and statistically analyzed using SPSS version 29 (SPSS Inc., Chicago, IL).

Results: Mean G8 score was 12.98 ± 2.61 (7-17). No statistically significant differences were noted in patients' QoL when assessed before starting sorafenib treatment and during follow-up. A worse G8 score was significantly associated with poorer physical function, as measured by TUGT, in all three encounters. Moreover, lower G8 scores were significantly correlated with worse QoL subscale scores during most follow-up encounters. Additionally, worse G8 scores were correlated with greater side effects after 3 months of treatment.

Conclusion: In elderly patients with HCC, G8 can predict QoL and symptom burden during sorafenib treatment. These findings highlight the importance of incorporating frailty assessments into routine clinical practice to guide personalized care for this vulnerable population.

Keywords: G8, quality of life, EORTC QLQ-C15-PAL, Egyptian elderly, HCC, sorafenib

Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most prevalent malignancy and the second leading cause of cancer-related mortality globally (1). It is, in fact, the fourth most prevalent cancer in Egypt (2). Aging is widely recognized as a risk factor for the development of HCC (3). Recent studies indicate a notable age-specific increase in HCC incidence (4). Elderly patients are considered "frail" owing to comorbidities, altered pharmacokinetics, and increased susceptibility to adverse effects of chemotherapy or surgical interventions (5).

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Curative interventions, including surgery, transplantation, and ablation, are unavailable to most patients with HCC because of their frequent diagnosis at advanced stages. Liver-directed therapy and oral targeted medications are employed in these individuals to extend survival and alleviate symptoms of malignancy and concomitant liver impairment. Consequently, assessing quality of life (QoL) is crucial to ascertain whether the treatment fulfilled its objective of palliation (6).

The most commonly used oral targeted therapy is sorafenib. Vascular endothelial growth factor receptors (-1, -2, and -3) and platelet-derived growth factor receptor-beta are inhibited by sorafenib, an oral multikinase tyrosine kinase inhibitor that targets the rapidly accelerated fibrosarcoma/mitogen-activated protein kinase/extracellular signal-regulated kinase pathway to inhibit tumour cell proliferation and angiogenesis and induce tumour cell apoptosis (7). Patients with intermediate HCC or Barcelona clinic liver cancer (BCLC) stage C who are not candidates for, or have not responded to, locoregional therapies, particularly those with Child-Pugh Class A liver disease, are generally recommended to receive sorafenib (8). International health authorities approved sorafenib after randomised, phase III, multicenter, double-blind, placebo-controlled trials verified its effectiveness in treating HCC. Among patients with well-preserved liver function (Child-Pugh A), these trials showed a statistically significant improvement in overall survival and time to progression compared with placebo. In these studies, sorafenib was well tolerated (9).

However, data on the safety and efficacy of sorafenib in older HCC patients are limited, and current treatment guidelines for the disease do not recommend specific procedures for older patients (10). Recent research indicates a higher prevalence of adverse health effects among older adults, resulting in a diminished QoL (11). Consequently, additional research on the QoL and tolerability of Sorafenib in the older Egyptian population is essential. Furthermore, forecasting the symptom burden in older adults is crucial for preventing adverse outcomes. Comprehensive techniques such as G8 provide a superior assessment of older adults and may predict patients' QoL during cancer therapy (12).

The primary objective of this research was to assess the G8 frailty tool as a predictor of QoL in a sample of Egyptian older patients with HCC receiving sorafenib. Our secondary aim was to assess the correlation between G8 and side effects and decompensation on sorafenib treatment.

Materials and Methods

From February 2023 to April 2024, this prospective cohort study was conducted at the HCC outpatient clinics of Ain Shams University Hospitals. In compliance with the the Declaration of Helsinki, ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Ain Shams University (approval number: FMASU R76/2023, date: 09.04.2024).

Sample Size and Power Calculation

A formal sample size calculation was conducted before the start of the study. A minimum of 51 patients were required to detect a small-to-moderate effect size (0.2) in changes in European Organization for Research and Treatment of Cancer Quality of Life 15 items Questionnaire for Palliative Care scores (EORTC QLQ-C15-PAL) across three time points (baseline, 1 month, and 3 months) using a repeated-measures analysis of variance (ANOVA) with 80% power and a significance level of 0.05. This calculation assumed a correlation among repeated measures of 0.5 and a non-sphericity correction of 1. To account for possible dropouts, the sample size was increased by 20%, resulting in a target of approximately 58 participants.

In addition, the sample size was sufficient to evaluate the discriminatory ability of the G8 score to predict treatment discontinuation of sorafenib treatment, assuming a 20% discontinuation rate and an area under the curve of 0.80, based on a two-sided Z-test with 80% power and α=0.05.

A total of 58 patients were enrolled. Forty patients completed the full 3-month follow-up, which was considered adequate to ensure statistical validity for the study's primary and secondary objectives.

Study Participants

Subjects aged 60 years or older with a verified diagnosis of HCC were included. According to the European Association for the Study of the Liver (EASL) guidelines, the diagnosis of HCC was made using imaging criteria (triphasic computed tomography or dynamic magnetic resonance imaging) or, for cases with atypical imaging results, by hepatic focal lesion biopsy with histopathology (13,14).

To be eligible for systemic therapy (sorafenib), they had preserved liver function (Child-Pugh stage A or B7) and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

Regarding their tumor staging on the BCLC staging system, they were classified as either BCLC C (with extrahepatic metastasis and/or portal vein invasion) or BCLC B (diffuse, infiltrative, bilobar HCC), regardless of whether they were treatment-naïve or had progressed/failed on other treatment modalities. In cases of unconfirmed portal vein invasion, abdominal Doppler was performed to confirm it.

Patients were excluded if they had a history of decompensation, hepatic encephalopathy, or neuropsychiatric disorders. Before starting treatment, baseline upper GI endoscopy was performed, with intervention as indicated. One hundred patients were assessed; however, only 58 met the study inclusion criteria (Figure 1).

Treatment Protocol

Our study participants received sorafenib for HCC according to the standard regimen recommended by the EASL (13,14). Sorafenib was prescribed at an initial dose of 400 mg twice daily, with monitoring for side effects and tolerability; liver function tests and enzyme measurements were performed weekly for the first month and then monthly. The dose was reduced to 200 mg twice daily or discontinued in the event of intolerability or side effects (13,14).

Adverse events were monitored throughout the treatment period and classified according to the common terminology criteria for adverse events, version 5.0.

History and Laboratory Investigations

Data collection included a detailed history of disease onset and course, prior viral hepatitis, antiviral therapy received, previous HCC treatments, and comorbidities. Moreover, patients underwent complete blood counts, liver function tests, including liver enzymes, and alpha-fetoprotein (AFP) measurements at the start of treatment and after three months.

Frailty assessment by G8 before the first dose: The G8 screening tool comprises seven components related to dietary intake, weight loss, mobility, neuropsychological issues, body mass index, prescription medications, and self-assessed health. It is derived from the Mini-Nutritional Assessment questionnaire and is designed specifically for older adults with cancer (15). A cut-off value of 14 shows high sensitivity for predicting the need for a complete geriatric assessment and indicates an elevated risk of frailty (15).

Assessment of quality of life before the first dose, after one month, and after three months:

Authorization to use the Arabic version of the EORTC QLQ-C15-PAL was obtained from the EORTC.

A popular, validated, translated, and published measure for assessing symptoms and QoL in cancer patients, the EORTC QLQ-C15-PAL is a reduced, 15-item version of the EORTC QLQ-C30 (16). It includes overall QoL; symptom measures (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, and constipation); and functional scales (including emotional scales) (16). The scale used to quantify the responses ranged from 0 to 100. It can be used in an outpatient setting with high patient volume. Elevated emotional, functional, and overall QoL ratings indicate a favorable QoL, whereas increased symptom and exhaustion scores reflect a greater symptom burden (16).

Assessment of physical function and Gait before the first dose, after one month, and after three months:

Timed up and go test (TUGT) is a straightforward assessment of an individual's mobility, necessitating both static and dynamic balance. It measures the time required for an individual to stand up from a chair, walk three meters, turn 180 degrees, walk back to the chair, and sit down after performing a second 180-degree rotation. During the assessment, the individual is required to wear their customary footwear and use any mobility assistance they typically need (17).

Statistics

• Data were tabulated and statistically analyzed using SPSS, version 20 (SPSS Inc., Chicago, IL).

• Quantitative data were presented as mean ± standard deviation. The independent t-test was used to compare quantitative data between independent groups. Repeated-measures ANOVA and paired t-tests were used to compare quantitative data over time.

• Qualitative data were expressed as frequencies (n) and percentages (%). Fisher's exact test and the chi-square test were used to assess the association between qualitative variables. The McNemar test and the Marginal Homogeneity test were used to compare qualitative data over time.

• The Pearson correlation coefficient (r) test was used to assess the correlation between two quantitative variables greater than zero indicates a positive relationship, while a value less than zero signifies a negative relationship (values were interpreted as follows: 0 no correlation, $0.0 < r < 0.30$ as weak, $0.30 < r < 0.70$ as moderate, $0.70 < r < 1.0$ as strong, and 1.0 as perfect correlation).

• A p-value ≤0.05 was considered significant.

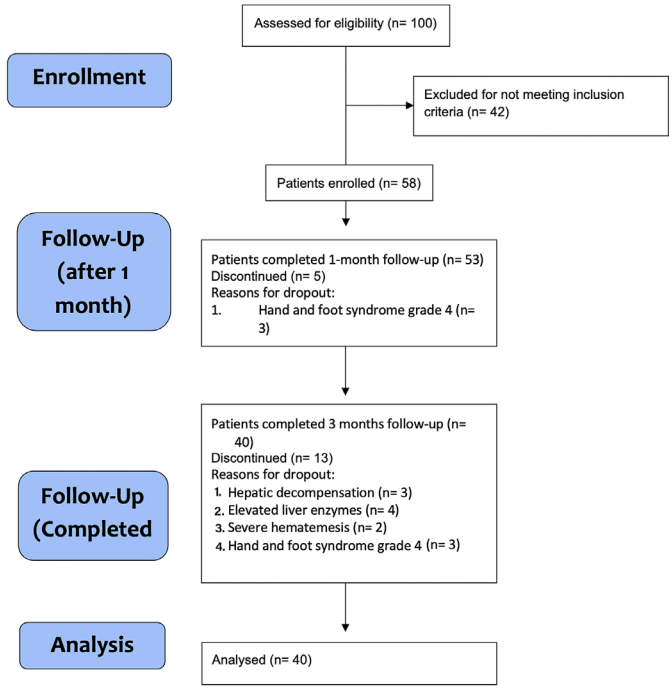

Figure 1. Inclusion of patients.

Results

Demographic Data and Disease Characteristics of the Studied Patients

Patient characteristics are presented in Table 1. Among the 58 included patients, the mean age was 67 years, and approximately 79% (n = 46) were male.

58.6% (n = 34) had comorbidities, with a mean Charlson Comorbidity Index of 11.5.

77.6% (n = 45) had post-hepatitis C cirrhosis, 36.2% (n = 21) were HCC treatment-naïve, and 82.7% (n = 48) were Child-Pugh A. Regarding tumor staging, 82.8% (n = 48) were classified as BCLC C. In addition, 86.2% (n = 50) had a baseline ECOG score of 1. The mean G8 score was 12.98 ± 2.61 (range: 7-17).

Quality of Life by EORTOC QLQ C15 PAL, TUGT, and Tumor Characteristics

As shown in Table 2, among the 58 included patients, 40 completed 3 months of treatment and follow-up. Dropouts were due to severe hematemesis in two patients; three patients developed grade IV hand-foot syndrome. Three patients developed decompensation, four developed elevated liver transaminase levels (>5 times the upper limit of normal), and six missed follow-up visits. A high rate of dropout in studies is expected in elderly with HCC due to a decline in functional reserve and metabolic alterations leading to higher rates of drug interactions and adverse effects (18). Mean TUGT increased significantly after 3 months of treatment, from 9.66 ± 1.75 seconds to 10.3 ± 1.73 seconds (p = 0.000) (Table 2).

Functional scores and overall QoL measured by the EORTC QLQ-C15-PAL were 89.4 ± 17.91 (40-100) and 59.96 ± 19.18 (16-100) at baseline, and increased to 90.88 ± 12.76 (40-100) and 64.58 ± 13.75 (33.3-83) after 3 months; these changes were not statistically significant. Symptom, fatigue, and emotional scores did not differ significantly during the follow-up period. At baseline, the mean AFP level was 26,228.98 ± 177,509.04 ng/mL (range, 2-1,352,775 ng/mL). 60.3% (n = 35) had vascular invasion, involving the main or branch portal vein; 36.2% (n =

Table 1. Demographic data and disease characteristics in the studied patients.

		n	%
Demographics			
Age mean ± SD (min-max)		67.59 ± 7.29 (60–93)	
Sex	Female	12	20.70%
	Male	46	79.30%
Comorbidities	No	24	41.40%
	Yes	34	58.60%
Mean Charlson Index mean ± SD (min-max)		11.55 ± 1.84 (7–15)	
Comorbidities and clinical history			
Duration of chronic hepatitis (years) mean ± SD (min-max)		7.32 ± 4.53 (1-20)	
Past hepatitis C virus treatment	No	13	22.40%
	Yes	45	77.60%
Past hepatitis B virus treatment	No	58	100.00%
	Yes	0	0.00%
Steroid, azathioprine for autoimmune hepatitis		1	1.70%
Unknown (cryptogenic)		12	20.70%
Hepatocellular carcinoma (HCC) status Duration of HCC (months) mean ± SD (min-max)		16.92 ± 21.36 (0–84)	
Previous HCC treatment	No treatment	21	36.20%
	TACE	14	24.10%
	Multiple TACE	11	19.00%
	RFA	2	3.40%
	Combined TACE ± RFA	4	6.90%
	TARE	1	1.70%
	SBRT	2	3.40%
	Liver transplantation	2	3.40%
	Resection	1	1.70%

Table 1. Continued.

		n	%
Demographics			
Symptoms	Asymptomatic	14	24.10%
	Fatigue	14	24.10%
	Abdominal pain	27	46.60%
	Anorexia	1	1.70%
	Nausea and vomiting	0	0.00%
	Weight loss	1	1.70%
	Abdominal distension	1	1.70%
	Jaundice	0	0.00%
	Fever	0	0.00%
Liver function and endoscopy findings			
Child score	A5	35	60.30%
	A6	13	22.40%
	B7	10	17.20%
UGI Findings (OV varices)	No	25	43.10%
	Grade I-II OV	19	32.80%
	Grade III-IV or risky OV	14	24.10%
PHG in UGI	No	22	37.90%
	Yes	36	62.10%
Clinical and performance characteristics			
BCLC	BCLC-0	0	0.00%
	BCLC-A	0	0.00%
	BCLC-B	10	17.20%
	BCLC-C	48	82.80%
ECOG at 0	0	1	1.70%
	1	50	86.20%
	2	7	12.10%
G8 at 0 mean ± SD (min-max)		12.98 ± 2.61 (7–17)	

SD: Standard deviation, min: Minimum, max: Maximum, ECOG: Eastern Cooperative Oncology Group, HCC: Hepatocellular carcinoma, UGI: Upper gastrointestinal endoscopy, BCLC: Barcelona Clinic Liver Cancer, TACE: Trans arterial chemoembolization, TARE: Trans arterial chemoembolization, SBRT: Stereotactic body radiotherapy, RFA: Radiofrequency ablation, OV: Esophageal varices, PHG: Portal hypertensive gastropathy.

21) had metastatic abdominal lymph nodes; and 27.6% (n = 16) had extrahepatic spread other than to abdominal lymph nodes, indicating that a patient may have more than one site of metastasis (Figure 2, Table 2).

At the third month of treatment, 75% of patients developed grade I or II side effects, compared with 49.1% after the first month; this difference was statistically significant (p = 0.007). The incidence of decompensation was slightly higher at the third month of treatment (17.5%) compared with the first month (10.9%); this difference was not statistically significant (p = 0.063) (Table 3).

At the end of the study (month 3), 69% (n = 40) of patients were evaluated for treatment response. Twenty-three patients (57.5%) had stable disease, five (12.5%) had a partial response, and twelve (30%) progressed during treatment, as shown in Table 3.

Correlation between G8 and Quality of life and TUGT

As shown in Table 4, G8 had a statistically significant negative correlation with TUGT at baseline and at each follow-up through the 3-month treatment period, with p-values of 0.000, 0.000, and 0.003, respectively, indicating that worse G8 scores were associated with poorer physical function.

Regarding QoL, G8 showed a statistically significant positive correlation with functional and emotional scores before treatment and at the first follow-up (1 month).

Symptom scores were negatively correlated with G8 at baseline, at 1 month, and at the final follow-up (3 months). The fatigue subset had a negative correlation with G8 at the start and after 3 months, with p-values of less than 0.001 and 0.042, respectively.

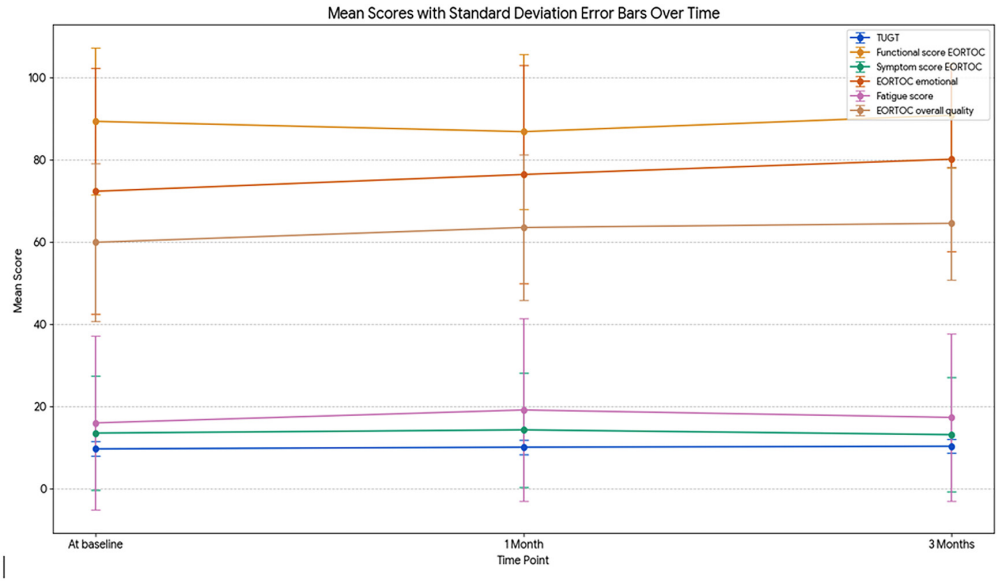

Figure 2. The longitudinal changes in timed up and go test and overall quality-of-life scores over the 3-month period.

TUGT: Timed up and go test, EORTOC: European Organisation for Research and Treatment of Cancer Quality of life questionnaire.

At baseline and at 1 and 3 months of follow-up, there were statistically significant positive associations between overall QoL and G8 (p = 0.000, 0.031, and 0.009, respectively).

G8 and Side Effects, Decompensation, and Treatment Response

In Table 5, patients' baseline G8 was lower in patients who developed side effects and decompensation later, with a statistically significant difference (p-value: 0.052) in patients who developed side effects at the third month of treatment, and therefore, G8 may predict patients' drug tolerability. Baseline G8 was lower in patients who could not continue treatment for 3 months. In contrast, G8 was higher in patients who had partial response and stable disease, with a borderline statistically significant difference (p = 0.054).

In Table 6, patients were classified according to scores of G8.

Patients who scored lower on the G8 (frailer) had higher (worse) symptom and fatigue scores at baseline (p = 0.002 and p = 0.011, respectively). They also had significantly lower emotional and overall well-being scores.

After the first month of treatment, patients with lower baseline G8 scores had significantly worse scores in all EORTC subsets, except for fatigue, which was worse but not statistically significant.

Similarly, after 3 months of treatment, patients with worse G8 scores at baseline showed significantly worse scores in all EORTC subsets, except for the functional score, which was worse but not statistically significant.

Frailty (low G8 score) is associated with poorer QoL, greater symptom burden, and increased fatigue over time. The orange bars, representing patients with higher G8 scores, tend to maintain higher scores and better overall outcomes. This underscores the importance of geriatric assessment tools, such as G8, in oncology: they help identify patients who may need tailored treatment or supportive care (Figure 3).

Discussion

HCC is a serious public health issue in Egypt. The government's mass screening program for HCV identification and treatment may contribute to Egypt's rising rates of HCC detection (19). Moreover, incidence has increased significantly in older age groups. Sorafenib is among the most frequently used agents for treating HCC, particularly in advanced stages; however, its effect on the QoL of older Egyptian adults remains understudied. Moreover, predicting of symptom burden and QoL before treatment in older adults is of utmost importance because frailty is more prevalent in this population. G8 has been evaluated in multiple studies as a predictor of frailty and increased symptom burden (12).

In the current study, the mean age of HCC patients was 67 years. Regarding the main findings of our study, the QoL in study subjects did not show a significant change after 1 and 3 months of treatment. Data on QoL with sorafenib treatment in the literature are scarce. However, Pereira et al. (20) showed worse QoL among patients treated with sorafenib compared with other treatment modalities, whereas Abraham et al. (21) reported better QoL in a relatively younger population (mean age 57 years).

Table 2. Quality of life, TUGT, and tumor characteristics at baseline and during treatment.

		At baseline		1 month		3 months		p-value
Functional and quality of life (QoL) scores								
TUGT		**9.66 ± 1.75 (6–16)**		**10.07 ± 1.72 (6–13)**		**10.3 ± 1.73 (8–14)**		**0.000***
Functional score EORTC		**89.4 ± 17.91 (40–100)**		**86.89 ± 18.84 (40–100)**		**90.88 ± 12.76 (40–100)**		**0.255**
Symptom score EORTC		**13.51 ± 13.85 (0–59)**		**14.29 ± 13.9 (0–59)**		**13.13 ± 13.93 (0–59)**		**0.403**
Emotional score EORTC		**72.38 ± 29.95 (0–100)**		**76.47 ± 26.58 (0–100)**		**80.19 ± 22.52 (17–100)**		**0.776**
Fatigue score EORTC		**15.99 ± 21.15 (0–66.7)**		**19.13 ± 22.22 (0–67)**		**17.32 ± 20.35 (0–66.6)**		**0.177**
The overall quality of life EORTC		**59.96 ± 19.18 (16–100)**		**63.57 ± 17.8 (16–83)**		**64.58 ± 13.75 (33.3–83)**		**0.610**
Laboratory parameters								
Hemoglobin (g/dL)		**12.61 ± 1.95 (8.7–18.7)**		**12.53 ± 2.63 (0–18.6)**		**12.62 ± 2.83 (0–18.3)**		**0.143**
White Blood cell (10^3/µL)		**6833.1 ± 2962.2 (1040–14700)**		**6139.36 ± 2758.57 (19–17700)**		**5394.44 ± 2770.44 (11–11800)**		**0.026***
Platelets (10^3/µL)		**190.55 ± 90.98 (42–495)**		**183.51 ± 93.97 (50–406)**		**168.63 ± 88.41 (58–419)**		**0.112**
AST aspartate aminotransferase (U/L)		**60.16 ± 40.31 (17–187)**		**70.15 ± 50.95 (26–243)**		**72.44 ± 55.03 (14–268)**		**0.289**
ALT alanine transaminase) (U/L)		**45.09 ± 33.63 (9–144)**		**48.51 ± 34.34 (14–200)**		**53 ± 45.53 (12–236)**		**0.495**
S.albumin (g/dL)		**3.73 ± 0.48 (2.76–4.7)**		**3.58 ± 0.44 (2.7–4.5)**		**3.61 ± 0.52 (2.5–4.7)**		**0.022***
S.bilirubin (mg/dL)		**0.95 ± 0.4 (0.34–2.6)**		**1.09 ± 0.54 (0.37–3)**		**1.12 ± 0.57 (0.5–3.8)**		**0.192**
INR		**1.16 ± 0.18 (0.95–1.89)**		**1.16 ± 0.19 (0.96–1.84)**		**0.82 ± 0.62 (0–2.1)**		**0.000***
Alpha feto protein AFP (ng/mL)		**26228.98 ± 177509.04 (2–1352775)**		**-**		**11009.49 ± 37924.21 (3.7–169521)**		**0.310**
Radiological and clinical features								
SLD		7.75 ± 4.98 (1-23.1)		-		6.73 ± 4.86 (1-21)		0.484
n		**At baseline**		**1 month**		**3 months**		**p-value**
		%	**n**	**%**	**n**	**%**		
Focal hepatic lesion number	Single	24	41.4%	-	-	17	42.5%	0.058
	Double	15	25.9%	-	-	6	15.0%	
	3 or more	19	32.8%	-	-	17	42.5%	
Focal hepatic lesion site	Lt lobe	8	13.8%	-	-	7	17.5%	0.317
	Rt lobe	37	63.8%	-	-	25	62.5%	
	Bilobar	13	22.4%	-	-	8	20.0%	
Vascular invasion	No	23	39.7%	-	-	14	35%	0.206
	Main branch	10	17.2%	-	-	11	27.5%	
	Rt or Lt branch	19	32.8%	-	-	13	32.5%	
	Segmental (main and branch)	6	10.3%	-	-	2	5%	

Table 2. Continued.

		At baseline		1 month		3 months		p-value
Lymph nodes	No	37	63.8%	-	-	26	65%	0.625
	Yes	21	36.2%	-	-	14	35%	
Extra hepatic spread (other than lymph. nodes)	No	42	72.4%	-	-	26	65%	1.000
	Yes	16	27.6%	-	-	14	35%	
Side effects	No	-	-	28	50.9%	10	25.0%	0.007*
	Yes	-	-	27	49.1%	30	75.0%	
Decompensation	No	-	-	49	89.1%	33	82.5%	0.063
	Yes	-	-	6	10.9%	7	17.5%	

*Highly significant. AFP: Alpha-fetoprotein, AST: Aspartate aminotransferase, EORTC QLQ-C15-PAL: EORTOC Quality of Life 15 items Questionnaire for Palliative Care.

Table 3. Distribution of treatment response after 3 months among the studied patients (m RECIST criteria).

		n	%
Treatment response	Lost	7	12%
	Stopped	11	19%
	PD	12	20.7%
	PR	5	8.6%
	SD	23	39.7%

PD: Progressive disease, PR: Partial response, SD: Stable disease, RECIST: Modified Response Evaluation Criteria in Solid Tumors.

In the current study, symptom and fatigue scores on the EORTC QLQ-C15-PAL were higher (worse) in patients aged 70 years or older, although the difference was not statistically significant. In a similar context, Marta et al. (22) examined adverse effects and toxicity rates in patients younger than 70 years compared with older patients and found no significant differences.

The correlation between the G8 score and QoL in HCC has not been extensively studied in the literature. In a study of prostate cancer patients, the G8 score showed significant positive correlations with functional score before the start of therapy, with emotional score at the start and after 1 month, with overall QoL at all three encounters. It also showed a negative correlation with symptom scores at the beginning and at every follow-up, and with fatigue scores at the beginning and after three months, according to Hamaya et al. (23). It also concluded that QOL was worse with G8 scores below 14, in line with our study.

According to another study by Ditzel et al. (24), G8 frailty and the QoL of patients with solid tumours were significantly correlated. It was concluded that lower QoL ratings are correlated with lower G8 scores.

Regarding G8 and the risk of adverse effects in elderly patients receiving sorafenib, our study concluded that G8 correlated with decompensation after one month of treatment and with adverse effects after three months. Other studies did not show a significant correlation between G8 scores and adverse events; for example, Sekiguchi et al. (25) concluded that worse G8 scores

Table 4. Correlation between G8 and quality of life and TUGT.

		G8 zero
TUGT 0	Pearson correlation	-0.543**
	Sig. (2-tailed)	0.000
TUGT 1	Pearson correlation	-0.524**
	Sig. (2-tailed)	0.000
TUGT 3	Pearson correlation	-0.462**
	Sig. (2-tailed)	0.003
Functional score EORTC 0	Pearson correlation	0.415**
	Sig. (2-tailed)	0.001
Functional score EORTOC 1	Pearson correlation	0.343*
	Sig. (2-tailed)	0.021
Functional score EORTC 3	Pearson correlation	0.008
	Sig. (2-tailed)	0.959
Symptom score EORTC 0	Pearson correlation	-0.558**
	Sig. (2-tailed)	0.000
Symptom score EORTC 1	Pearson correlation	-0.398**
	Sig. (2-tailed)	0.007
Symptom score EORTC 3	Pearson correlation	-0.454**
	Sig. (2-tailed)	0.003
EORTC emotional 0	Pearson correlation	0.370**
	Sig. (2-tailed)	0.004
EORTC emotional 1	Pearson correlation	0.313*
	Sig. (2-tailed)	0.036
EORTC emotional 3	Pearson correlation	0.253
	Sig. (2-tailed)	0.106
EORTC overall quality 0	Pearson correlation	0.511**
	Sig. (2-tailed)	0.000
EORTC overall quality 1	Pearson correlation	0.322*
	Sig. (2-tailed)	0.031
EORTC overall quality 3	Pearson correlation	0.396**
	Sig. (2-tailed)	0.009
Fatigue score 0	Pearson correlation	-0.454**
	Sig. (2-tailed)	0.000
Fatigue score 1	Pearson correlation	-0.266
	Sig. (2-tailed)	0.077
Fatigue score 3	Pearson correlation	-0.319*
	Sig. (2-tailed)	0.042

*,**Statistically significant, TUGT: Timed up and go test, EORTC: European Organization for Research and treatment of cancer.

did not correlate with survival or with adverse events associated with sorafenib.

While our study demonstrates the G8 tool's predictive value for QoL and toxicity in elderly Egyptian HCC patients, comparisons with international cohorts reveal important nuances. For instance, Williet et al. (11) reported a lower treatment discontinuation rate (15%) in frail European patients receiving sorafenib than our 31% attrition. This may reflect disparities in comorbidities (e.g., higher HCV prevalence in our population) or in access to early supportive interventions.

Table 5. G8 and side effects and decompensation and treatment response.

		G8 zero	p
Side effects 1 month	No	13.2+2.9 (7-17)	0.645
	Yes	12.9+2.3 (8-17)	
Side effects 3 months	No	14.6+2 (10-17)	0.052*
	Yes	13.1+2.1 (8-17)	
Decompensation 1 month	No	13.4+2.5 (7-17)	0.009*
	Yes	10.5+1.4 (9-12)	
Decompensation 3 months	No	13.5+2.2 (8-17)	0.655
	Yes	13.1+2 (11-17)	
Treatment response	Lost	9.7+3.1 (7-13)	0.054*
	Stopped	12+2.7 (8-17)	
	PD	13.4+2.7 (8-17)	
	PR	14.6+1.8 (12-17)	
	SD	13.7+2 (10-17)	

*: Statistically significant, PD:: Progressive disease, PR: Partial response, SD: Stable disease.

Notably, Sekiguchi et al. (25) found that G8 predicted survival but not adverse events in Japanese HCC patients, in contrast to our observed correlation between G8 and toxicity. This discrepancy could stem from variations in frailty cutoffs (e.g., G8 <14 vs. <12) or cultural differences in symptom reporting. However, our findings align closely with Ditzel et al. (24), in whose prospective Danish cohort G8 scores were linked to QoL deterioration across cancer types, reinforcing frailty's transdiagnostic impact.

These comparisons underscore that while G8 is a globally relevant screening tool, its operational thresholds and clinical implications may require regional calibration, particularly in high-burden settings like Egypt, where HCC etiology and healthcare infrastructure differ from high-income countries.

Taken together, these findings align with recent international evidence validating the G8 tool's utility in geriatric oncology. For instance, Sekiguchi et al. (25) demonstrated G8's prognostic value for treatment tolerability and survival in elderly patients with HCC receiving systemic therapy, while Ditzel et al. (24) confirmed its relevance for predicting QoL outcomes. Earlier work by Hamaya et al. (23) in prostate cancer also supported G8's predictive role across multiple QoL domains. Collectively, these studies highlight the G8 tool's global applicability; however, its

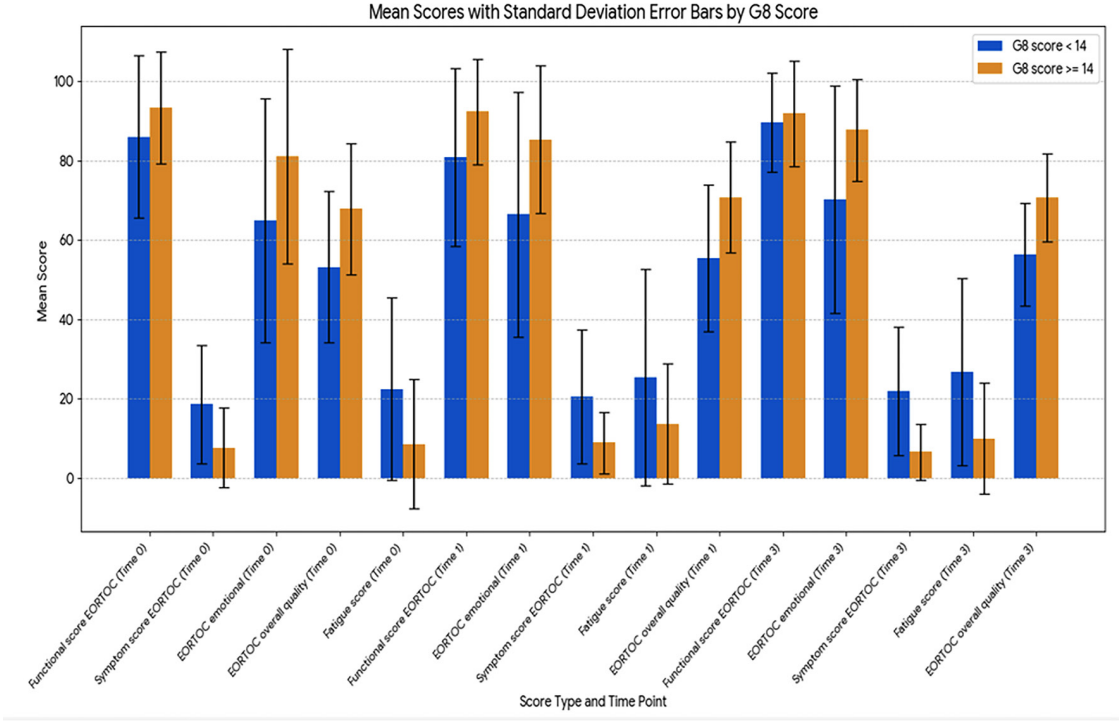

Figure 3. G8 scoring and quality of life domains along study course.

EORTOC: European Organisation for Research and Treatment of Cancer Quality of life questionnaire.

Table 6. Correlation between categories of G8 and quality of life, decompensation, and side effects in the third month.

		Below 14	G8 14 or more	p
		Mean ± SD (min–max)	Mean ± SD (min–max)	
Functional score EORTC 0		86 ± 20.4 (40–100)	93.3 ± 14 (57–100)	0.123
Symptom score EORTC 0		18.6 ± 14.9 (0–59)	7.7 ± 10 (0–33.3)	0.002*
EORTC emotional 0		64.9 ± 30.8 (0–100)	81 ± 27 (0–100)	0.041*
EORTC overall quality 0		53.2 ± 19 (16–83)	67.8 ± 16.5 (33.3–100)	0.003*
Fatigue score 0		22.4 ± 23 (0–66.7)	8.6 ± 16.2 (0–50)	0.011*
Functional score EORTOC 1		80.8 ± 22.4 (40–100)	92.3 ± 13.3 (40–100)	0.049*
EORTC emotional 1		66.4 ± 30.9 (0–100)	85.3 ± 18.6 (40–100)	0.020*
Symptom score EORTC 1		20.5 ± 16.8 (0–59)	8.9 ± 7.7 (0–25)	0.007*
Fatigue score 1		25.4 ± 27.3 (0–67)	13.7 ± 15.2 (0–50)	0.091
EORTC overall quality 1		55.5 ± 18.5 (16–83)	70.7 ± 14 (33.3–83)	0.003*
Functional score EORTC 3		89.6 ± 12.4 (60–100)	91.8 ± 13.2 (40–100)	0.583
EORTC emotional 3		70.2 ± 28.6 (17–100)	87.7 ± 12.8 (67–100)	0.024*
Symptom score EORTC 3		21.9 ± 16.1 (3.3–59)	6.6 ± 7 (0–25)	0.001*
Fatigue score 3		26.7 ± 23.6 (0–66.6)	10 ± 13.9 (0–50)	0.013*
EORTC overall quality 3		56.4 ± 12.9 (33.3–83)	70.7 ± 11.1 (50–83)	0.000*
Side effects at 3 months	No	1 (5.6%)	9 (40.9%)	0.013*
	Yes	17(94.4%)	13(59.1%)	
Decompensation at 3 months	No	13 (72.2%)	20 (90.9%)	0.211
	Yes	5 (27.8%)	2 (9.1%)	

An independent t-test was utilised. A p-value <0.05 was considered statistically significant. *: Statistically significant, SD: Standard deviation, EORTC: European Organization for Research and treatment of cancer, min: Minimum, max: Maximum.

operational thresholds and clinical implications may require local adaptation in high-burden settings, such as Egypt. Sekiguchi et al. (25) on G8's prognostic value in HCC patients receiving systemic therapy (Cancer Rep). Ditzel et al. (24) on G8 and QoL outcomes in geriatric oncology (Lancet Healthy Longevity). Hamaya et al. (23) on frailty and QoL in prostate cancer (Int J Clin Oncol).

Study Limitations

Several factors limit this study. First, although the sample size achieved the estimated statistical power, the relatively small sample may limit the generalizability of the findings. Second, the use of the abbreviated EORTC QLQ-C15-PAL, while practical for palliative settings, may have overlooked key QoL domains—such as social, cognitive, and financial aspects—that are captured by the full EORTC QLQ-C30. Third, due to the limited number of events, multivariable analyses (e.g., logistic regression) were not performed to assess the independent predictive value of the G8, thereby restricting our ability to control for potential confounders such as comorbidities, ECOG performance status, and Child-Pugh class.

A dropout rate of 31% was observed by the third month, primarily due to clinical deterioration, treatment intolerance, or loss to follow-up—challenges frequently encountered in elderly patients with advanced HCC. As a result, a per-protocol analysis was conducted, which may introduce attrition bias and further limit generalizability. Although comorbidities were assessed using the Charlson Comorbidity Index, other relevant factors such as socioeconomic status, psychosocial support, and access to care were not fully accounted for and may have influenced both treatment adherence and patient-reported outcomes.

Future studies with larger cohorts, comprehensive multivariable analyses, and the use of intention-to-treat approaches are warranted to validate and expand upon these findings.

While the dropout rate reflects real-world challenges in elderly patients with HCC, our analysis confirmed the validity of the retained cohort. Future work will address confounders such as socioeconomic status.

Conclusion

Worse G8 scores were consistently associated with poorer QoL, slower gait speed, and increased risk of treatment-related toxicity in elderly patients with HCC. These findings highlight the clinical utility of the G8 screening tool in identifying frail patients at higher risk of adverse outcomes during systemic therapy. Incorporating G8 into routine oncologic assessment

may support more individualized treatment strategies, including dose adjustments, enhanced supportive care, and closer monitoring. Additionally, G8 can facilitate informed decision-making by aligning treatment plans with patient frailty status and expectations.

Ethics

Ethics Committee Approval: In compliance with the the Declaration of Helsinki, ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Ain Shams University (approval number: FMASU R76/2023, date: 09.04.2024).

Informed Consent: Non required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.A., Concept: E.A., M.M.M.G., H.A., M.A.M., D.F., Design: E.A., M.M.M.G., H.A., M.A.M., D.F., Data Collection or Processing: E.A., D.F., Analysis or Interpretation: E.A., M.M.M.G., M.A.M., D.F., Literature Search: E.A., D.F., Writing: E.A., M.M.M.G., H.A., M.A.M., D.F.

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