ORIGINAL ARTICLE

Characteristics and prognosis of hepatocellular carcinoma patients after direct-acting antiviral hepatitis C virus therapy in a single medical center in Egypt

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ABSTRACT

Objective: Hepatocellular carcinoma (HCC) incidence has increased dramatically over the previous two decades and is anticipated to rise further in some countries, notably the United States, by 2030. HCC is most widespread in Asia and Africa, where hepatitis B and C are ubiquitous and lead to the development of chronic liver disease and, finally, HCC. In this study, we examined changes in the characteristics and prognosis of HCC patients, as well as the risk of developing HCC after direct-acting antiviral (DAA) medication.

Methods: The study enrolled all individuals who attended the Clinical Oncology and Nuclear Medicine Department, Suez Canal University Hospital, Ismailia, Egypt, with a proven diagnosis of HCC in the period between January 2020 and December 2021. HCC is diagnosed based on radiographic appearance (arterial enhancement phase and delayed washout phase) or compatible histology.

Results: This retrospective cohort included 254 HCC patients, separated into three groups. Kaplan-Meier curves with log-rank analysis revealed that hepatitis C virus (HCV) treatment therapy considerably reduced the time to HCC development following hepatitis diagnosis ($p < .001$). HCV therapy had a substantial impact on progression-free survival and overall survival in HCC patients ($p < .001$).

Conclusions: The emergence of DAA medication has greatly altered the management of HCV patients in the context of HCC. DAAs have been shown to be both safe and beneficial in these individuals, particularly in terms of lowering the risk of hepatic decompensation. DAAs have been reported to enhance overall survival in patients with cirrhotic HCV-related HCC, most likely due to decreased hepatic decompensation.

Key Words: Direct-acting antiviral therapy, Pegylated-interferon, Hepatitis C virus, Hepatocellular carcinoma

1. INTRODUCTION

Liver cancer was the sixth most prevalent disease and the third leading cause of cancer death worldwide in 2020, with an anticipated 905,677 new cases and 830,180 deaths. East Asia had the highest frequency, at 17.9 per 100,000 people (26.9 in men and 8.9 in women), followed by Micronesia, Northern Africa, Southeast Asia, and Melanesia. South-Central Asia had the lowest incidence (3.0 per 100,000),

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while South America had the highest (4.4 per 100,000).

In comparison, the incidence rate in Northern America was 6.9 per 100,000, while Western Europe had a rate of 5.6 per 100,000. Males are three times more likely than females to have liver cancer.[1]

Egypt is Africa's third and the world's fifteenth most populous country, respectively. Health officials in Egypt regard Hepatocellular carcinoma (HCC) as the most difficult health issue. The number of HCC patients more than doubled in a decade.[2]

HCC incidence has risen rapidly over the last two decades and is expected to climb even higher in several countries, particularly the United States, by 2030.[1]

HCC is most widespread in Asia and Africa, where hepatitis B and C are ubiquitous and lead to the development of chronic liver disease and, finally, HCC. Chronic alcohol consumption, hepatitis B and C, and non-alcoholic fatty liver disease are all significant risk factors for HCC.[3]

Some of the less common causes are Wilson's disease, familial hemochromatosis, alpha1-antitrypsin deficiency, primary biliary cirrhosis, and autoimmune hepatitis.[4, 5]

HCV infection is the leading cause of cirrhosis in the world (93%),[6] and it is also a risk factor for HCC.[7] It induces both hepatic inflammation and fibrosis. HCV protein expression promotes cell mutation and malignant transformation.[8, 9]

The increase in HCV prevalence may have prompted large-scale schistosomiasis treatment initiatives in Egypt in the 1950s and 1960s.[10]

Egypt has documented various degrees of HCV prevalence. HCV prevalence in the 15-59 age group was 14.7% in 2008, but dropped to 10% in 2015. This drop in frequency has been connected to the age of patients getting anti-schistosomal injections.[11]

Direct-acting antivirals (DAAs) have transformed the treatment of hepatitis C virus (HCV) infection, reaching high rates of sustained virological response (95%), all while retaining a good safety profile and high compliance rates.[12]

As a result, viral clearance was expected to reduce morbidity, mortality, and the risk of HCC. However, since 2016, there has been widespread worry over an unexpectedly high likelihood of HCC formation and recurrence following DAA treatment, prompting an avalanche of research with inconsistent findings.[11]

We investigated changes in the features and prognosis of HCC patients, as well as the pattern of HCC following DAA treatment or PI (pegylated interferon).

2. SUBJECT AND METHODS

2.1 Study design and participants

An analytical, record-based retrospective cohort research.

2.2 Procedure

: This study was conducted at Suez Canal University Hospital's (SCUH) Clinical Oncology and Nuclear Medicine Department in Ismailia, Egypt. Patients were identified using the department registry, and data was retrieved from medical records using a predetermined technique.

2.3 Patient selection and data collection

This study enrolled all patients attending the Clinical Oncology and Nuclear Medicine Department, Suez Canal University Hospital, Ismailia, Egypt, with a proven diagnosis of HCC in the period from January 2020 until December 2021. HCC was detected based on radiographic appearance by MRI abdomen using LI-RAD classification (arterial enhancement phase and delayed washout phase), elevated alpha-fetoprotein level, or pathological diagnosis.

The following information was gathered from patients' files.

- Data on demographics (age, sex)
- History of chronic illness (HTN, DM)
- Understanding liver disease etiology
- History of Alcohol Consumption and Smoking
- The patient complained at the time of presentation. Level of hepatic impairment and compensatory mechanisms (Child-Pugh classification)[13]
- ECOG performance status[14]
- At the time of the presentation, the staging systems were BCLC and AJCC[15]

The abdomen's radiological appearance on MRI was graded using the LI-RAD classification,[16] and the metastatic workup comprised a bone scan, computed tomography, chest, and pelvis with contrast.

- Tumor burden (including number of lesions, maximum diameter, presence of vascular invasion, lobes involved, and extrahepatic metastases if presented)
- Laboratory investigations at presentation, alpha-fetoprotein (AFP) levels, pathological grade, HCC-directed therapy, and response to first-line treatment based on RECIST criteria[17]
- Time to develop HCC after hepatitis diagnosis
- Progression-free survival and overall survival

Individual treatment decisions and post-diagnosis follow-ups were recorded. Surgical excision and local ablation ther-

apy (LAT), target therapy, and palliative care have all been identified as possibly curative therapies.

According to available laboratory data and clinical history, liver disease was classified as chronic hepatitis B, hepatitis C, alcohol-related liver disease, metabolic-associated fatty liver disease, and other causes. Patients with hepatitis B or C were classified as having viral HCC, while the others had non-viral HCC. Patients' demographics, HCC etiology, liver dysfunction, tumor burden, treatment, and survival rates were compared throughout time, as well as those with viral and non-viral HCC.

We evaluated the effectiveness, safety, and clinical outcomes of DAA-based treatment to PI (pegylated interferon) in HCV-infected patients who developed HCC.

2.4 Inclusion criteria

1. Age between 20 and 90 years.

2. All patients with a confirmed HCC diagnosis who visit the Clinical Oncology and Nuclear Medicine Department at Suez Canal University Hospital in Ismailia, Egypt, from January 2020 to December 2021.

2.5 Exclusion criteria

1. Patients with recurrent HCC.

2. Those who have liver cancer other than HCC, such as intrahepatic cholangiocarcinoma or metastatic liver cancers.

2.6 Sample size and sampling technique

Simple random selection was utilized to choose a research sample from all cancer patients who visited the Clinical Oncology and Nuclear Medicine Department at Suez Canal University Hospital in Ismailia, Egypt, between January 2020 and December 2021 who were diagnosed with HCC.

2.6.1 *Sample size*

The sample size was computed using the following equation 1:[18]

Where: • n = the sample size.

• $Z_{1-\frac{\alpha}{2}}$ = the confidence interval, which equals 1.96 when type 1 error is 5%.

• p = prevalence of HCC is up to 70.48% of all liver malignancies among Egyptians.

• d = absolute error or precision, usually equals 10%.

The determined sample size is (230) people. After adding the estimated drop-out rate (10%), the total sample size will be 254 participants.

2.7 Statistical analysis

The statistical analysis was conducted using SPSS version 28 (IBM Co., Armonk, NY, USA).

The Kruskal-Wallis test was used to quantitative data provided as medians and interquartile ranges. Categorical data were provided as frequency and percentage, and they were evaluated using the Chi-square test or Fisher's exact test, as applicable.

To compare the survival distributions of various groups, the Kaplan-Meier curve was coupled with a log rank test.

3. Results

The retrospective cohort study involved 254 HCC patients. Patients were divided into three groups according to the previous therapy they received for HCV, as follows:

• Group I included 82 unvaccinated patients (32.3%).

• Group II consisted of 146 (57.5%) patients who had received Sovaldi after previous vaccination (DAA group).

• Group III included 26 patients (10.2%) who had previously been immunized and administered PEGylated interferon (PI group).

3.1 Baseline patients' characteristics

48 patients (58.5%) in group I, 87 patients (59.6%) in group II, and 9 patients (34.6%) in group III were between 60 and 70 years old. Age was significantly different among the three groups ($p < .001$), as patients who received PI (PI group) were significantly older than those who received Sovaldi (DAA group) and the unvaccinated patients (group I).

67 patients (81.7%) in group I, 111 patients (76%) in group II, and 21 patients (80.8%) in group III were males. 84 patients (57.5%) in the DAA group presented with a history of chronic illness (51.4% were hypertensive and 21.2% were diabetic). Out of 254 HCC patients included in the study, 19 patients only gave a history of alcohol consumption, and 82 patients were smokers (see Table 1).

The most common complaint among the study groups was abdominal pain (51.2%, 52.1%, and 65.4% in groups I, II, and III, respectively). Abdominal distension differed statistically substantially between groups ($p = .005$), with the PI group having a much higher prevalence than the DAA group and unvaccinated patients (group I). Additionally, hematemesis was significantly different among groups ($p = .019$), being significantly less prevalent among the DAA group than group I.

Liver status was significantly different among the studied groups ($p < .001$), as the DAA groups and PI group presented

significantly with fewer manifestations of liver decompensation than group I.

The ECOG performance status at the time of initial presentation varied significantly among the examined groups ($p < .001$), with lower scores in the DAA and PI groups than in Group I.

143 patients in the DAA group (97.9%) presented with a history of hepatitis C virus infection, with a statistically significant difference among the studied groups ($p < .001$). 7 patients in group I presented with a history of non-viral hepatitis, and 8 patients presented without a history of hepatitis, with a statistically significant difference among the studied groups (p values of .015 and .001, respectively) (see Table 1).

3.2 Clinical assessment and staging at the time of diagnosis

Liver status was significantly different among the studied groups ($p < .001$), as the DAA groups and PI group presented significantly with fewer manifestations of liver decompensation than group I.

Table 1. Baseline characteristics of the studied groups

	Group I (n = 82)	Group II (n = 146)	Group III (n = 26)	p value
Age (years)				
40 to 50	4 (4.9%)	12 (8.2%)	0 (0%)	< .001*
> 50 to 60	17 (20.7%)	33 (22.6%)	4 (15.4%)	
> 60 to 70	48 (58.5%)	87 (59.6%)	9 (34.6%)	
> 70 to 80	13 (15.9%)	14 (9.6%)	11 (42.3%)	
> 80 to 90	0 (0%)	0 (0%)	2 (7.7%)	
Sex				
Male	67 (81.7%)	111 (76%)	21 (80.8%)	.577
Female	15 (18.3%)	35 (24%)	5 (19.2%)	
Chronic illness				
No	46 (56.1%)	62 (42.5%)	10 (38.5%)	.097
Yes	36 (43.9%)	84 (57.5%)	16 (61.5%)	
HTN	31 (37.8%)	75 (51.4%)	13 (50%)	.136
DM	18 (22%)	31 (21.2%)	9 (34.6%)	.317
Alcohol consumption	7 (8.5%)	8 (5.5%)	4 (15.4%)	.19
Smoking	24 (29.3%)	46 (31.5%)	12 (46.2%)	.263
Patients Complaint				
Nausea	6 (7.3%)	15 (10.3%)	2 (7.7%)	.732
Vomiting	6 (7.3%)	17 (11.6%)	3 (11.5%)	.57
Abdominal pain	42 (51.2%)	76 (52.1%)	17 (65.4%)	.416
Distension	12 (14.6%)	15 (10.3%)	9 (34.6%)	.005*
Yellowish discoloration of the sclera	8 (9.8%)	5 (3.4%)	1 (3.8%)	.128
Melena	6 (7.3%)	7 (4.8%)	0 (0%)	.339
Poor oral feeding	17 (20.7%)	30 (20.5%)	4 (15.4%)	.819
Regurgitation	1 (1.2%)	7 (4.8%)	2 (7.7%)	.211
Hematemesis	11 (13.4%)	5 (3.4%)	2 (7.7%)	.019*
Constipation	10 (12.2%)	23 (15.8%)	4 (15.4%)	.76
Accidently discovered, asymptomatic	2 (2.4%)	7 (4.8%)	0 (0%)	.418
Coma, disturbed level of consciousness	5 (6.1%)	2 (1.4%)	0 (0%)	.089
Ascites	3 (3.7%)	1 (0.7%)	0 (0%)	.154
Itching	1 (1.2%)	2 (1.4%)	0 (0%)	> .999
Abdominal discomfort	6 (7.3%)	23 (15.8%)	2 (7.7%)	.133
Cachexia	4 (4.9%)	2 (1.4%)	0 (0%)	.237
Diarrhea	2 (2.4%)	3 (2.1%)	0 (0%)	> .999
Underlying liver disease				
HBV	3 (3.7%)	3 (2.1%)	0 (0%)	.593
HCV	66 (80.5%)	143 (97.9%)	26 (100%)	< .001*
Non-viral hepatitis	7 (8.5%)	2 (1.4%)	0 (0%)	.015*
No hepatitis	8 (9.8%)	0 (0%)	0 (0%)	.001*

Note. Data are presented as frequency (%), *: Statistically significant as p value < .05, Different lower-case letters indicate significant difference, HTN: Hypertension, DM: Diabetes mellitus

The ECOG performance status at the time of initial presentation varied significantly among the examined groups ($p < .001$), with lower scores in the DAA and PI groups than in Group I.

39 patients (47.6%) from group A were BCLC stage C at the time of diagnosis. 66 patients (45.2%) from the DAA group and 11 patients (42.3%) from the PI group were BCLC B at the time of the initial diagnosis.

Table 2. Clinical and radiological assessment of the studied groups

	Group I	Group II	Group III	*p* value
Liver status				
Compensated	53 (64.6%)	123 (84.2%)	24 (92.3%)	< .001*
Decompensated	29 (35.4%)	23 (15.8%)	2 (7.7%)	
Portal vein				
Patent	55 (67.1%)	118 (80.8%)	22 (84.6%)	.038*
Thrombosed	27 (32.9%)	28 (19.2%)	4 (15.4%)	
Tumor burden				
One lesion	22 (26.8%)	42 (28.8%)	9 (34.6%)	
Two lesions	18 (22%)	43 (29.5%)	6 (23.1%)	.617
Three lesions	11 (13.4%)	23 (15.8%)	3 (11.5%)	
Multiple lesions	31 (37.8%)	38 (26%)	8 (30.8%)	
Maximum tumor diameter (cm)	7.5 (4.48-11)	5.5 (4-9.35)	5.75 (3-8.48)	.013*
Lobes involved				
Right	39 (47.6%)	81 (55.5%)	15 (57.7%)	
Left	4 (4.9%)	7 (4.8%)	1 (3.8%)	.83
Both	39 (47.6%)	58 (39.7%)	10 (38.5%)	
Presence of vascular invasion	27 (32.9%)	28 (19.2%)	4 (15.4%)	.038*
Extrahepatic metastasis	22 (26.8%)	19 (13%) [b]	5 (19.2%)	.034*
Site of metastasis				
Bone	10 (12.2%)	10 (6.8%)	3 (11.5%)	.361
Lung	3 (3.7%)	3 (2.1%)	0 (0%)	.593
Brain	0 (0%)	0 (0%)	0 (0%)	-
Lymph nodes	12 (14.6%)	10 (6.8%)	2 (7.7%)	.148
Other sites	1 (1.2%)	2 (1.4%)	0 (0%)	> .999
ECOG performance status				
1	21 (25.6%)	75 (51.4%)	9 (34.6%)	
2	44 (53.7%)	62 (42.5%)	17 (65.4%)	< .001*
3	17 (20.7%)	9 (6.2%)	0 (0%)	
BCLC staging				
A	17 (20.7%)	40 (27.4%)	8 (30.8%)	
B	23 (28%)	66 (45.2%)	11 (42.3%)	.006*
C	39 (47.6%)	32 (21.9%)	7 (26.9%)	
D	3 (3.7%)	8 (5.5%)	0 (0%)	
AJCC staging				
I	16 (19.5%)	34 (23.3%)	7 (26.9%)	
II	11 (13.4%)	31 (21.2%)	6 (23.1%)	.025*
III	24 (29.3%)	57 (39%)	7 (26.9%)	
IV	31 (37.8%)	24 (16.4%)	6 (23.1%)	
Child Pugh classification				
A	27 (32.9%)	79 (54.1%)	15 (57.7%)	
B	33 (40.2%)	56 (38.4%)	10 (38.5%)	< .001*
C	22 (26.8%)	11 (7.5%)	1 (3.8%)	
Radiological appearance				
Definitive HCC	34 (41.5%)	75 (51.4%)	5 (19.2%)	.007*
Multiple HFL suggesting HCC	48 (58.5%)	72 (49.3%)	21 (80.8%)	.01*
Splenomegaly	7 (8.5%)	18 (12.3%)	7 (26.9%)	.048*
Ascites	13 (15.9%)	17 (11.6%)	3 (11.5%)	.645
Cirrhotic liver features	65 (79.3%)	142 (97.3%)	25 (96.2%)	< .001*

Note. *: Statistically significant as *p* value < .05, Different lower-case letters indicate significant difference, ECOG: Eastern Cooperation Oncology Group, BCLC: British Columbia Lottery Corporation, AJCC: American Joint Committee on Cancer, HCC: Hepatocellular carcinoma, HFL: Hepatic focal lesion, HTN: Hypertension, DM: Diabetes mellitus

31 patients (37.8%) from group A were stage IV according to AJCC staging, while 57 patients (39%) were stage III. In the PI group, 7 patients (26.9%) presented with stages I and III according to the AJCC staging system.

The BCLC and AJCC staging systems differed considerably between groups (p = .006, .025, respectively), with significantly less progressive staging in the DAA and PI groups compared to group I.

According to the Child Pugh classification, 33 patients (40.2%) in Group I were Child A, while 79 and 15 patients (54.1% and 57.7%, respectively) were Child A in the DAA and PI groups.

The study groups showed significantly different Child Pugh classifications (p < .001), as it was significantly lower in the DAA and PI groups (see Table 2).

3.3 Radiological appearance of the studied groups

41.5%, 51.4%, and 19.2% of patients in groups I, II, and III, respectively, showed definite HCC features. LI-RADS 5 MRI abdomen and sonographic indications of HCC. 58.5%, 49.3%, and 80.8% presented with LI-RAD 3 and 4 by MRI abdomen. 18 patients (12.3%) in the DAA group presented with splenomegaly.

Definitive HCC (LI-RADS 5 by MRI abdomen) and multiple HFLs suggesting HCC (LI-RAD 3 and 4 by MRI abdomen) were present at significantly different rates among the study groups (p = .007, .01, respectively), as the prevalence of definitive HCC (LI-RAD 5 by MRI abdomen with contrast) was significantly lower, while that of multiple HFLs suggesting HCC (LI-RAD 3 and 4 by MRI abdomen) was significantly higher among the PI group than the DAA group and group I.

Furthermore, the number of instances triggering splenomegaly differed considerably between groups (p = .048), with the PI group having a much greater rate than group I.

We also noted a statistically significant difference among groups regarding portal vein status (p = .038), as the DAA group included a lower proportion of patients eliciting thrombosed portal veins than Group I. Additionally, the three groups were significantly different in terms of tumor size (p = .013), which was significantly smaller in the vaccinated groups (DAA group and PI group). Vascular invasion and extrahepatic metastasis were substantially different between groups (p = .038 and .034, respectively), with DAA having considerably lower rates than Group I.

In the DAA group, 142 patients (97.3%) had radiological evidence of liver cirrhosis in their MRI abdomen. Also, liver cirrhosis prevalence significantly differed among groups (p < .001), being significantly lower in group I (see Table 2).

3.4 Laboratory and pathological examinations of the examined groups

In terms of laboratory investigations, the median ALT was 65.5, 59, and 45.5 in groups I, II, and III, respectively (the P value was 0.057). The median AST was 80.5, 61.5, and 72.5 in groups I, II, and III, respectively (p = .029).

Median total albumin was 3, 3.1, and 3.25 in groups I, II, and III, respectively, with a statistically significant difference (p = .006).

Total and direct bilirubin were different among the studied groups. For total bilirubin, the median level was 1.58 in group I, 1.54 in group II, and 1.1 in group III (p = .026), whereas for direct bilirubin, the median level was 0.8 in group I, 0.8 in group II, and 0.65 in group III (p = .1).

AST, albumin, and total bilirubin levels differed considerably across groups (p < .05). Patients in the DAA group had significantly lower AST levels compared to group I.

Moreover, albumin levels were significantly higher in both the DAA and PI groups than in group I, while there was a significant drop in total bilirubin levels in the PI group compared to the DAA group and group I.

Out of 254 HCC patients included in the trial, 131 were pathologically confirmed to have HCC, with no statistically significant difference between the three study groups (p = .54). The remaining patients were diagnosed radiologically and had elevated alpha-fetoprotein levels.

Median alpha-fetoprotein was 289, 400, and 350 in groups I, II, and III, respectively (p = .659).

56 patients in the studied sample presented pathologically as HCC grade III, with no statistically significant difference among the three studied groups regarding pathological grade (p = .367).

3.5 Time to develop HCC after hepatitis diagnosis dependent on previous HCV treatment

Kaplan-Meier curves with log-rank analysis were utilized to assess the time to HCC development after hepatitis diagnosis between study groups. Kaplan-Meier curves with log-rank analysis showed that HCV treatment therapy significantly affected time to HCC development after hepatitis diagnosis (p < .001). Patients who received DAA therapy or PEG (PEGylated)-interferon had a mean (95% CI) of 24.28 years (23.61 to 24.96) and 26.42 years (24.9 to 27.95), respectively, than unvaccinated patients (mean = 20.24 years, 95% CI: 19.36 to 21.12), with a hazard ratio (95% CI) of 0.44 (0.31

to 0.62) and 0 (see Figure 1).

3.6 HCC therapy for the examined groups

Table 3 shows that treatment by local ablative (TACE and RFA), target, and palliative therapy differed substantially between groups ($p < .001$). The DAA and PI groups used local ablative and target treatments more frequently than group I. On the other hand, the DAA and PI groups had considerably lower rates of palliative treatment than group I.

Following first-line treatment, assessment revealed that the patients had achieved a complete response according to RECIST criteria, which varied substantially among the investigated groups ($p = .005$), with patients in the DAA group having a significantly higher response rate than group I.

Table 3. HCC treatment of the studied groups

	Group I ($n = 82$)	Group II ($n = 146$)	Group III ($n = 26$)	*p* value
Surgical intervention	0 (0%)	3 (2.1%)	0 (0%)	.383
Local ablative therapy	9 (11%)	60 (41.1%)	9 (34.6%)	< .001*
Target therapy	41 (50%)	125 (85.6%)	19 (73.1%)	< .001*
Chemotherapy	21 (25.6%)	30 (20.5%)	11 (42.3%)	.056
Palliative therapy	47 (57.3%)	29 (19.9%)	4 (15.4%)	< .001*
Response after first-line treatment				
Complete response	0 (0%)	16 (11%)	1 (3.8%)	.005*
Partial response	22 (26.8%)	62 (42.5%)	10 (38.5%)	.063
Stable disease	20 (24.4%)	46 (31.5%)	11 (42.3%)	.199
Progressive disease course	41 (50%)	23 (15.8%)	4 (15.4%)	< .001*

Note. *: Statistically significant as *p* value < .05

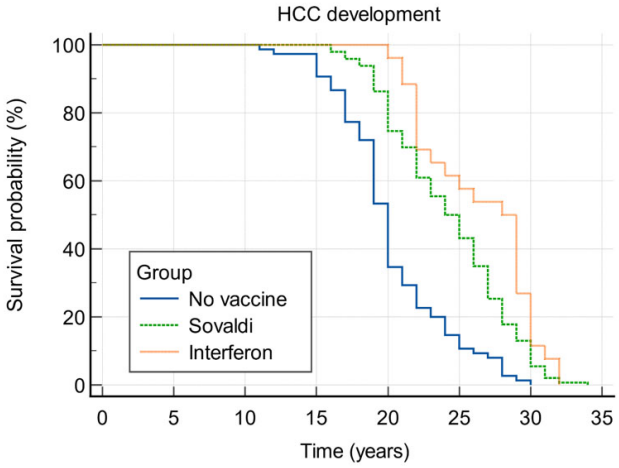

Figure 1. Kaplan-Meier curves for time to HCC development after hepatitis diagnosis according to HCV treatment therapy

3.7 Progression-free survival study of HCC patients after first-line treatment

Kaplan-Meier curves with log-rank analysis showed that HCV therapy significantly affected progression-free survival of HCC patients ($p < .001$). HCC progression took longer in the DAA group (median = 13 months, 95% CI: 10 to 16) and PI group (median = 10 months, 95% CI: 7 to 19) than in the unvaccinated group (median = 7 months, 95% CI: 6 to 8), with hazard ratios (95% CI) of 0.53 (0.39 to 0.73) and 0.51 (0.33 to 0.8) in the DAA and PI groups, respectively (see Figure 2).

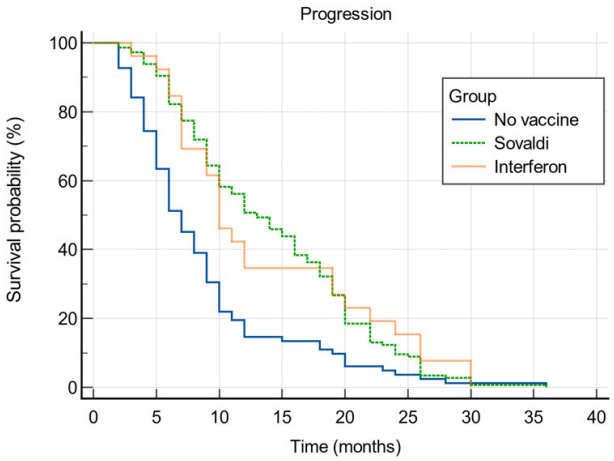

Figure 2. Kaplan-Meier curves for progression free survival analysis of HCC patients according to DAA therapy

3.8 Overall survival study of HCC patients following HCV treatment

Based on Kaplan-Meier curves and log-rank analysis, HCV therapy had a statistically significant impact on the survival

of HCC patients ($p < .001$). The estimated mean survival of patients in the DAA group (36.51 months, 95% CI: 34.43 to 38.6) and the PI group (34.78 months, 95% CI: 29.56 to 39.99) was longer than that of the unvaccinated (24.37 months, 95% CI: 20.94 to 27.81), with a hazard ratio (95% CI) of 0.31 (0.18 to 0.52) and 0.4 (0.18 to 0.91) in the DAA (see Figure 3).

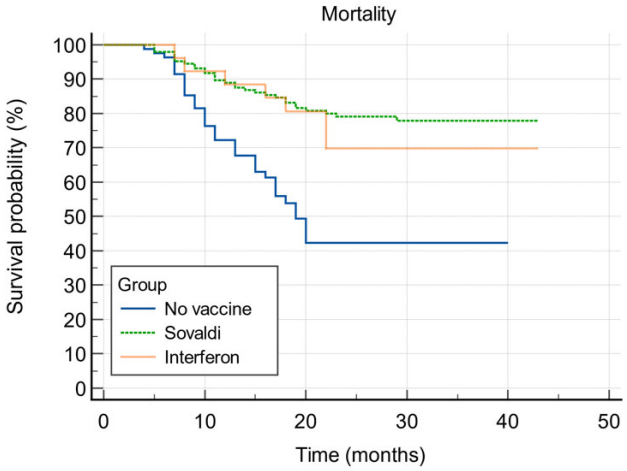

Figure 3. Kaplan-Meier curves for overall survival analysis of HCC patients according to HCV therapy

4. Discussion

Hepatitis C virus (HCV) infection is a major risk factor for hepatocellular carcinoma (HCC).

Direct-acting antivirals (DAAs) are safe, well-tolerated, cost-effective, and provide a cure for almost all patients with HCV.

Although HCV eradication with DAAs has demonstrated advantages such as fibrosis regression, better liver function and portal hypertension, and a lower risk of all-cause death, it is still contentious for patients with active or treated HCC.

These results go beyond previous reports, showing that there is a male predominance between different groups with an age between 60 and 70 years. This finding is consistent with prior research, where the average age at HCC diagnosis was 62.8 ± 10.2 years.[19] The group was predominately male (79%).

In our study, we also noticed a statistically significant difference in portal vein status across groups, with the DAA group having a lower proportion of patients with thrombosed portal veins than the unvaccinated group. Furthermore, tumor size differed considerably between the three groups, with the vaccinated groups (DAA and PI) having much smaller tumors. The prevalence of vascular invasion and extrahepatic metastases varied greatly between groups, with DAA having much lower rates than the unvaccinated group.

In the DAA group, 142 patients (97.3%) had radiological evidence of liver cirrhosis in their MRI abdomen. The prevalence of liver cirrhosis was considerably lower in the unvaccinated group compared to other groups.

However, few studies have found a significant link between past DAA usage and aggressive illness. The study found that infiltrative PVT, HCC pattern, and regional lymph node metastasis were all considerably increased.

There was a significant difference ($p < .05$) between HCC patients treated with DAA and those who did not get it. Following DAA treatment, HCC patients experienced increased malignant portal vein invasion and local dissemination via malignant lymphadenopathy.[20] Another prospective study found substantial multifocal and infiltrative HCC patterns following DAA therapy.[21] According to Romano et al., patients with aggressive malignancies experience quicker tumor progression after HCV treatment, including more nodules and extra-hepatic metastases.[22]

When comparing our findings to those of other research, it should be noted that DAA medication is related to enhanced overall survival in HCV patients with HCC. In our study, HCV therapy significantly improved HCC patient survival ($p < .001$). Patients in the DAA group (mean survival of 36.51 months) and PI group (mean survival of 34.78 months) outlived those in the unvaccinated group (mean survival of 24.37 months). This is similar to findings from prior A subgroup investigations of HCV patients, DAA recipients, and those who achieved SVR12, which demonstrated significant impacts on OS. Patients with and without HCV had similar survival rates. The median OS was 20.7 months compared to 17.4 months. HCV patients who used DAAs had a median OS of 71.8 months, compared to 11. months for those who did not take DAAs.[23]

A study of 328 HCV cirrhotic individuals with early HCC found that the probability of mortality differed considerably based on the initial incidence, early decompensation, or early HCC recurrence. Patients with early hepatic decompensation episodes showed worse survival rates than those with early HCC recurrence. The researchers showed that the survival of cirrhotic HCV-untreated patients with effectively treated early HCC is mostly driven by hepatic decompensation, showing that HCV eradication after DAAs may increase overall survival by protecting liver function. A prospective multicenter study investigated the role of DAAs in the survival of patients with HCV-related compensated cirrhosis and their initial HCC diagnosis.[23]

5. Conclusion

DAA medication has significantly impacted the management of HCV patients with HCC. DAAs were discovered to be both safe and helpful in these individuals, particularly in lowering the risk of hepatic decompensation. In this vein, the good effect on liver function may enhance the feasibility of curative therapies for early HCC, ultimately leading to a large and well-documented advantage in lengthening the overall life of patients with treated early HCC. The pathophysiology of HCC following HCV treatment is poorly known. Understanding the molecular pathways that cause HCC may help to identify new biomarkers for early diagnosis.

Study limitation

Some limitations in our study stem from its retrospective nature; a selection bias cannot be totally removed. Another drawback was that our investigation was a single center-based study with a small number of patients, preventing accurate matching between the study groups in terms of equivalent staging and hence proper comparison.

Also, this study was concerned about all patients attending at this time period, either newly diagnosed or previously diagnosed, which made some difference between study groups.

A major limitation in the current study was the incompliance of some patients with regular follow-ups and the unavailability of some information, so we resorted to contacting patients by phone calls. As a result, we recommend that future studies include a larger sample size and a longer follow-up period.

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Authors contributions

MMA and SHS contributed to the conception and design of the work. MMA, WSAA, and SHS contributed to the collection of data from the filling system. MMA and SHS contributed to the acquisition, analysis, and interpretation of the data. MMA and SHS revised and supervised the work. SHS and MMA wrote the initial draft of the manuscript. All authors contributed to manuscript revision. All authors approved the final version of the manuscript.

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Conflicts of Interest Disclosure

The authors declare they have no conflicts of interest.

Informed consent

The research ethics committee of the Faculty of Medicine at Suez Canal University (FOMSCU) approved the final protocol. Clinical data was collected after approval from the patients' filling system. Confidentiality of the information and patient privacy were considered, and no personal data was published.

Ethics approval

The Publication Ethics Committee of the Sciedu Press. The journal's policies adhere to the Core Practices established by the Committee on Publication Ethics (COPE).

Provenance and peer review

Not commissioned; externally double-blind peer reviewed.

Data availability statement

Data will be used only in that research; this is beside the fact that patients' contact information was required in order to minimize the problems of inaccurate recording and follow-up visits.

Data sharing statement

No additional data are available.

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