

# Survival Outcome and Prognostic Factors Among Patients With Hepatocellular Carcinoma: A Hospital-Based Study

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## ABSTRACT

**BACKGROUND:** Hepatocellular carcinoma (HCC) is a leading cancer with very high incidence and mortality and low survival rate in Vietnam and worldwide. This study aimed to investigate the survival outcome and its prognostic factors among HCC patients.

**METHODS:** This is a retrospective descriptive study on patients newly diagnosed with HCC at Hanoi Oncology Hospital, Vietnam from January 2018 to December 2020. Overall survival (OS) was calculated by the Kaplan-Meier method. Log-rank test and Cox regression were used to investigate the association among patients' OS and their diagnosis and treatment factors.

**RESULTS:** A total of 674 patients were included. The median OS was 10.0 months. The survival rates at 6, 12, 24, and 36 months were 57.3%, 46.6%, 34.8%, and 29.7%, respectively. The initial performance status (PS), Child-Pugh score, and Barcelona Clinic Liver Cancer (BCLC) stage at the time of diagnosis are prognostic factors of HCC OS. A total of 451 (66.8%) patients have died, most of them (375 equally 83.1%) died at home, and only 76 (16.9%) died at hospital. Hepatocellular carcinoma patients living in the rural area more likely died at home than those living in the urban area (85.9% vs 74.8%,  $P = .007$ ).

**CONCLUSIONS:** Hepatocellular carcinoma has a poor prognosis with low OS. Performance status, Child-Pugh score, and BCLC stage were the independent prognostic factors for the survival outcome of HCC patients. The fact that most HCC patients died at home suggested that home-based hospice care needs to be paid special attention.

**KEYWORDS:** Hepatocellular carcinoma, survival outcome, overall survival, prognostic factors, place of death (POD)

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## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related death worldwide in both sexes.<sup>1</sup> There is a disparity in the global distribution of the HCC burden, with HCC patients in Asian Pacific countries account for more than a half of the global HCC patients.<sup>2</sup> Even though cancer treatment has achieved great improvement in recent years, HCC prognosis is still poor with limited overall survival (OS) time and survival rate in both developing and developed countries.<sup>3–6</sup>

In Vietnam, HCC is the leading cancer in both incidence and cancer mortality.<sup>7</sup> With the high prevalence of hepatitis B virus (HBV), 12.3% in men and 8.8% in women, chronic HBV infection is still the main risk factor of HCC in Vietnam.<sup>8</sup> Moreover, HCC patients tended to be diagnosed at the late stage and their number gradually increased over the year.<sup>9,10</sup> Although there have been studies on the epidemiology, risk factors, and clinical characteristics of HCC in Vietnam, no

studies on the survival outcome and its prognostic factors of HCC patients have ever been conducted, even though they are extremely important to help find effective interventions to reduce the HCC burden.

Hepatocellular carcinoma is a complex and heterogeneous disease. Commonly, a patient with HCC is accompanied by cirrhosis and chronic viral hepatitis.<sup>11</sup> Cancer patients at the terminal stage may face many challenges, not only physical discomfort but also psychosocial distress. At that stage, HCC patients often have a variety of symptoms such as abdominal pain, ascites, edema, variceal hemorrhage, hepatic encephalopathy, fatigue, and cachexia.<sup>12,13</sup> Notably, HCC has ranked the sixth out of 14 types of cancer in prevalence rate of distress.<sup>14</sup>

Beside the need of physical symptom control and mental health care, being able to die at a preferred place is one of the essential needs of terminally ill cancer patients.<sup>15–19</sup> The results of surveys from different countries have shown that most cancer patients preferred to die at home.<sup>20–23</sup> Dying at home has been associated with greater benefits to achieve a “good death” for patients and greater satisfaction for family members.<sup>24–26</sup>

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However, in Vietnam, choosing to die at home also exposes patients and their families to the challenge of ongoing hospice care due to the absence of health care providers. Currently, the modern hospice care model has grown rapidly around the world, especially in developed countries. It has helped improve the quality of life for end-stage cancer patients. Unfortunately, it has not yet been applied much in developing countries like Vietnam, due to limited resources and lack of a clear policy framework and related guidelines.

In this study, in addition to evaluating the survival outcome and prognostic factors among HCC patients, we also collected and analyzed data related to HCC patients' place of death (POD) and compared the difference between the urban and rural areas. These data may contribute to improve the quality of life of HCC patients through the development of home-based palliative and hospice care services in the near future.

## Methods

### *Inclusion criteria*

All patients who were newly diagnosed with HCC at our hospital from January 2018 to December 2020 were included. Hepatocellular carcinoma diagnosis was confirmed based on the Guidelines of Vietnam Ministry of Health for the Diagnosis and Treatment of Hepatocellular Carcinoma (latest edition—2020).<sup>27</sup>

### *Exclusion criteria*

- Patients with any lacking of targeted information.
- Patients having other cancer than HCC.

### *Study design*

This is the descriptive study using retrospective data.

### *Sampling method*

Convenient sampling—all of HCC patients whose medical records are suitable for inclusion criteria and did not have any exclusion criteria were selected.

### *Data source*

Data were obtained from the hospital electronic medical record database.

### *Outcomes*

- Primary outcome: HCC patients' OS.
- Secondary outcome: factors related to OS.
- Tertiary outcome: actual POD of HCC patients.

### *Variable definition and classification*

- Collected data on major clinical characteristics of HCC patients included age, performance status (PS), viral

hepatitis status (HBV, hepatitis C virus [HBC]), severity of cirrhosis (Child-Pugh score), alpha-fetoprotein (AFP) level, tumor size, portal vein thrombus (PVT), and Barcelona Clinic Liver Cancer (BCLC) stage.

- Initial treatment modalities were classified as follows: curative surgery (hepatectomy), radiofrequency ablation (RFA), transarterial chemoembolization (TACE), targeted therapy, chemotherapy, and best supportive care (BSC).
- OS was defined as the length of time from either the date of diagnosis or the start of treatment to death from any cause. Patients who were either still alive or lost to the last follow-up (December 31, 2021) were censored.
- Information about the patient's condition (dead or alive) and patient's POD was obtained through telephoning or mailing to patient's next of kin.

### *Statistical analysis*

Data were input via EpiData (version 3.1). Statistical analyses were performed with SPSS version 20.0. Descriptive statistics were calculated for categorical variables using frequencies and proportions. The Kaplan-Meier method was used to estimate OS. The log-rank test was used to evaluate differences between the 2 groups in OS, whereas the Cox proportional hazards models were used for multivariate analysis. *P* value of less than .05 was considered statistically significant.

## Results

### *Clinical characteristics of the study population*

There were totally 674 HCC patients included in the study. Their clinical characteristics were presented in Table 1. Male patients were predominant with 86.9% (male:female ratio was 6.6:1). The average age was 59.8 ( $\pm 11.7$ ) years old (range = 16–89), majority of patients were from 40 to 59 years old (42.3%), whereas the youngest age group who diagnosed at <40 years old had the lowest proportion (4.6%).

At the time of initial diagnosis, majority of patients have PS 0–1 (78.3%). There were 542 patients (80.4%) had positive viral hepatitis, in which HBV infection only was 75.8%, HCV only was 3.9%, and co-infection HBV and HBC was 0.7%. Child-Pugh A had the highest proportion (66.7%); Child-Pugh B and C were found in 24.3% and 8.9% of patients, respectively.

There were 574 patients (85.2%) who had a high level of AFP at the initial diagnosis; the median level of AFP was 568.8 ng/mL. The median diameter of liver tumor was 69.2  $\pm$  38.7 mm, and the largest tumor has the diameter of 197 mm. The proportion of patients with PVT was 28.3%. In BCLC stage, BCLC C had the highest proportion (35.3%), followed by BCLC A (30.1%) and BCLC B (24.5%), and BCLC 0 and D had very low proportions (1% and 9.1%, respectively).

Regarding primary treatment modalities, there were 123 patients (18.2%) declining treatment. Among those receiving treatment, BSC and TACE were the dominant modalities with

**Table 1.** Clinical characteristics of the study population.

CHARACTERISTICS	N (%)
Sex	
Men	586 (86.9)
Women	88 (13.1)
Age (years)	
Mean $\pm$ SD	59.8 $\pm$ 11.7
<40	31 (4.6)
40–59	285 (42.3)
60–69	220 (32.6)
$\geq$ 70	138 (20.5)
PS	
0	125 (18.5)
1	403 (59.8)
2	124 (18.4)
3	21 (3.1)
4	1 (0.1)
Viral hepatitis	
No viral hepatitis	132 (19.6)
HBsAg (+)	511 (75.8)
Anti-HCV (+)	26 (3.9)
HBsAg (+) plus anti-HCV (+)	5 (0.7)
Child-Pugh score	
A5	323 (47.9)
A6	127 (18.8)
B7	74 (11.0)
B8	54 (8.0)
B9	36 (5.3)
C	60 (8.9)
AFP level	
Within normal limits	100 (14.8)
High	574 (85.2)
PVT	
Yes	191 (28.3)
No	483 (71.7)
BCLC stage	
0	07 (1.0)

(Continued)

**Table 1.** (Continued)

CHARACTERISTICS	N (%)
A	203 (30.1)
B	165 (24.5)
C	238 (35.3)
D	61 (9.1)
Primary treatment modality	
BSC	233 (34.6)
Chemotherapy	45 (6.7)
Targeted therapy	52 (7.7)
TACE	176 (26.1)
RFA	14 (2.1)
Hepatectomy	31 (4.6)
Declined treatment	123 (18.2)

Abbreviations: AFP, alpha-fetoprotein; anti-HCV, anti-hepatitis C virus; BCLC, Barcelona Clinic of Liver Cancer; BSC, best supportive care; HBsAg, hepatitis B surface antigen; PS, performance status; PVT, portal vein thrombus; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

34.6% and 26.1% patients, respectively; other methods had much lower patient proportions (targeted therapy 7.7%, chemotherapy 6.7%, hepatectomy 4.6%, and RFA 2.1%).

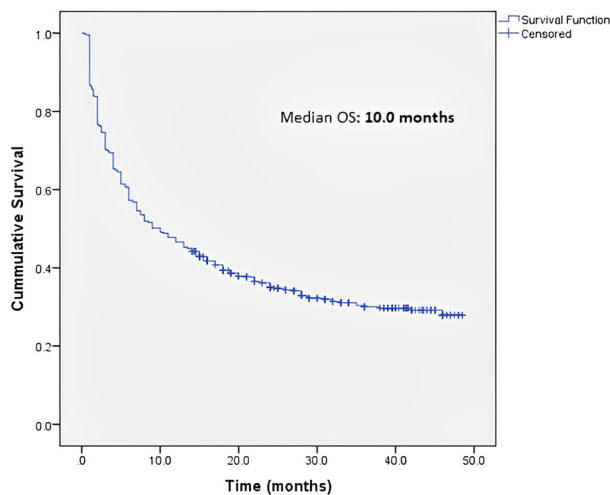
#### Overall survival

The OS situation of HCC patients in the study was presented in Figure 1. The median OS was 10.0 months [95% confidence interval (CI) = 7.8–12.2 months]. The survival rates at 6, 12, 24, and 36 months were 57.3%, 46.6%, 34.8%, and 29.7% respectively.

#### Factors related to the survival outcome

The differences in HCC patients' OS by their characteristics were shown in Table 2. The log-rank test showed that the following factors had a significant association with HCC patients' OS: PS ( $P < .001$ ), Child-Pugh score ( $P < .001$ ), AFP level ( $P < .01$ ), tumor size ( $P < .01$ ), PVT ( $P < .001$ ), BCLC stage ( $P < .001$ ), and primary treatment modalities ( $P < .001$ ). However, there were no statistical differences in OS by sex ( $P = .081$ ), age group ( $P = .093$ ), and viral hepatitis status ( $P = .15$ ). Figure 2 illustrated the difference of survival rate in different BCLC stages.

As shown in Table 3, the result from Cox regression analysis confirmed that the independent prognostic factors for HCC OS were PS ( $P < .001$ , hazard ratio [HR] = 1.7, 95% CI = [1.4–2.0]), Child-Pugh score ( $P = .001$ , HR = 1.1, 95% CI = [1.0–1.2]), and BCLC stage ( $P < .001$ , HR = 1.5, 95% CI = [1.3–1.8]).



**Figure 1.** The OS curve of HCC patients. OS indicates overall survival; HCC, hepatocellular carcinoma.

### Place of death

Among 451 deceased HCC patients, majority (375 patients [83.1%]) died at home, whereas only 76 patients (16.9%) died in hospital. This difference was statistically significant ( $P < .001$ , chi-square test). This trend appeared in both urban and rural groups, but the proportion of died-at-home patients in the rural group was significantly higher than that of the urban group (85.9% vs 74.8%,  $P = .007$ , odds ratio [OR] = 2.05 [1.21–3.47]), as showed in Table 4.

## Discussion

### Hepatocellular carcinoma patients' survival outcome

In this study, the HCC patients' median OS was 10.0 months. This finding was quite similar to studies on HCC patients in other countries, including Charonpongsuntorn's<sup>5</sup> study in Thailand (OS was 8.9 months), Wang and Li's<sup>3</sup> study in China (9.0 months), as well as Goutte et al's<sup>4</sup> study in France (9.4 months), and Giannini et al's<sup>28</sup> study in Italy (9.0 months). Recently, Reveron-Thornton et al<sup>6</sup> conducted a meta-analysis of 110 studies from 1980 to 2017, showing that the 5-year OS and recurrence-free survival (RFS) of HCC patients after resection were only 56.2% and 35.2%, respectively and that the 5-year OS and 5-year RFS have not been improved significantly over time.

When investigating the OS rates at 12, 24, and 36 months of HCC patients in this study, the respective data were 46.4%, 34.8%, and 29.7%. We found that this result was relatively similar to that of Wang and Li's<sup>3</sup> study (OS rate at 12 and 24 months were 39.3% and 35.3%, respectively) and Goutte et al's<sup>4</sup> study (OS at 12, 24, and 36 months were 45.4%, 31.3%, and 22.8%, respectively). Thus, HCC remains a poor prognostic disease with a modest median OS, not only in developing countries but also in developed countries, where treatment

modalities, health services, and quality of care are considered much more advanced. This could be due to most HCC patients were not diagnosed at early stage, and the systemic therapies for advanced-stage HCC have not yet made breakthrough in the past years.

In the period of 2018 to 2020, sorafenib was the mainstay drug for HCC at the advanced stage and has been shown to improve OS when comparing with using best supportive care alone.<sup>29–31</sup> However, in Vietnam, health insurance only covers 50% of sorafenib treatment and the cost of sorafenib is still too high for most Vietnamese people. Therefore, its affordability is the main and biggest barrier for most of HCC patients. In this study, there were only 7.7% HCC patients treated with sorafenib, whereas there were up to 34.6% HCC patients receiving best supportive care alone.

Noticeably, the proportion of HCC patients who declined treatment in this study was relatively high, 28.2%. There might be many reasons that could lead patients to refusing treatment. First, most of patients with HCC, as well as with other common cancers in Vietnam, were diagnosed at the advanced stage, which was considered by many people as too late for any treatment.<sup>32</sup> Second, misconceptions about cancer still widely exist,<sup>33</sup> and third, hopelessness and low fighting spirit are not uncommon when patients receive the cancer diagnosis.<sup>34</sup> All of those could lead patients to turning down any treatment recommendations or selecting unorthodox methods such as traditional herbs, macrobiotic, instead of accepting orthodox medical methods at hospital.

Surprisingly, the OS of patients who declined treatment was 6.5 months, better than the targeted therapy group (6.0 months) or BSC group (2.5 months) as shown in Table 2. The main reason for this seemingly strange finding is the difference in the BCLC stage of the declined treatment group, with the number of patients at the advanced stage (BCLC C) or end stage (BCLC D) was only 39.0%, significantly lower than that of the targeted group (53.8%) or the BSC group (76.8%) with  $P < .05$ . Studies in different countries have confirmed the crucial prognostic value of the BCLC stage, the higher the BCLC stage is, the shorter the survival time is.<sup>3,5,35</sup>

### Prognostic factors of the HCC survival outcome

PS at the time of diagnosis of HCC is not only a factor to classify the HCC stage according to the BCLC criteria<sup>36</sup> but also an important factor to determine the adequate treatment modality. Therefore, the PS at the initial diagnosis could affect HCC patients' OS. In this study, PS was a strong independent prognostic factor for the median OS of HCC patients. The worse the PS is, the lower the median OS is ( $P < .001$ , HR = 1.7, 95% CI = [1.4–2.0]).

Chronic HBV infection has been known to be the leading risk factor for HCC.<sup>37–39</sup> Globally, HBV infection was responsible for approximately 50%–70% of HCC cases<sup>40</sup> and 33% of

**Table 2.** Median OS by sex, age, PS, viral hepatitis status, Child-Pugh score, BCLC stage, and primary treatment modalities.

CHARACTERISTICS	OS (MONTHS)	[95% CI]	P VALUE
All patients	10.0	[7.8–12.2]	
Sex			
Men	9.0	[6.8–11.2]	.081
Women	16.0	[8.2–23.8]	
PS			
0			<.001
1	13.0	[9.8–16.2]	
2	2.0	[1.8–2.2]	
3	1.0		
4	1.0		
Age group (years)			
<40	3.0	[0.0–6.3]	.093
40–59	9.0	[5.4–12.7]	
60–69	11.0	[5.8–16.2]	
≥70	10.5	[4.8–16.2]	
Viral hepatitis			
No viral hepatitis B and C	10.0	[4.0–16.0]	.15
HBsAg (+)	10.0	[7.4–2.6]	
Anti-HCV (+)	5.5	[0.0–13.6]	
HBsAg (+) plus anti-HCV (+)	2.0		
Child-Pugh score			
A5	22.0	[14.2–9.8]	<.001
A6	10.0	[5.6–14.4]	
B7	7.0	[4.0–10.0]	
B8	2.5	[1.9–3.1]	
B9	2.0	[1.0–3.0]	
C	1.0	[0.9–1.1]	
AFP (ng/mL)			
<400	20.0	[15.9–24.1]	<.001
≥400	5.0	[4.1–5.9]	
Tumor size (cm)			
≤5	24.0	[15.5–32.5]	<.001
>5	6.0	[4.7–7.3]	
PVT			
No	18.0	[14.3–1.6]	<.001

(Continued)



Table 2. (Continued)

CHARACTERISTICS	OS (MONTHS)	[95% CI]	P VALUE
Yes	3.0	[2.0–4.0]	
<b>BCLC stage</b>			
0			<.001
A	42.0		
B	13.5	[9.0–18.0]	
C	4.0	[3.1–4.9]	
D	1.0	[0.9–1.1]	
<b>Primary treatment modalities</b>			
BSC	2.5	[2.1–2.9]	<.001
Chemotherapy	11.0	[3.2–18.0]	
Targeted therapy	6.0	[4.8–7.2]	
TACE	36.0		
RFA			
Hepatectomy			
Declined treatment	6.5	[3.2–9.8]	

Abbreviations: AFP, alpha-fetoprotein; anti-HCV, anti-hepatitis C virus; BCLC, Barcelona Clinic of Liver Cancer; BSC, best supportive care; CI, confidence interval; OS, overall survival; HBsAg, hepatitis B surface antigen; PS, performance status; PVT, portal vein thrombus; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

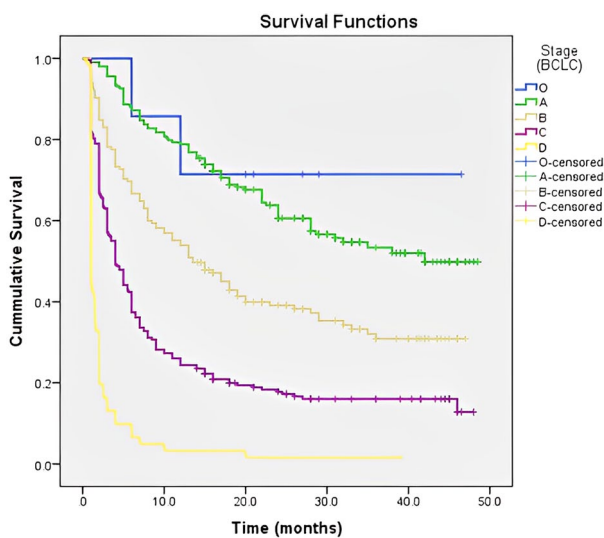


Figure 2. The OS curves of different BCLC stages. BCLC indicates Barcelona Clinic Liver Cancer; OS, overall survival.

HCC mortality.<sup>41</sup> In this study, the prevalence of positive HBsAg was 78.6%, similar to that of Le et al's<sup>9</sup> study, in which the prevalence of positive HBsAg among HCC patients in 3 central hospitals in the Northern region of Vietnam was 81.3%. Although chronic viral hepatitis infection (B and/or C) is a major risk factor for HCC, its association with HCC patients' OS was not statistically significant in this study ( $P = .15$ ).

Portal vein thrombus is considered one of the poor prognostics in HCC, especially in HCC patients with major PVT.<sup>42</sup> In this study, PVT was strongly and negatively associated with OS ( $P < .001$ ) in the univariate analysis by the log-rank test. However, PVT was not an independent prognostic factor for OS in the multivariate analysis using the Cox model, adjusted for PS, Child-Pugh score, BCLC stage, and primary treatment modalities. This result may be explained by a number of reasons. First, the sample size was quite small. Second, most HCC patients in this study was at advanced stage, which is the reason of the poor survival prognosis. This may lead to under appreciation of PVT prognostic value in multivariate analysis adjusted for BCLC stage. In fact, PVT was a significantly independent prognostic factor for OS when we removed BCLC stage from the multivariate analysis. Plus, we did not have information on the grades of PVT. Several studies showed that the HCC patients with the more severe PVT grade had the worse prognosis for OS.<sup>43,44</sup>

In addition to the cancer burden, HCC patients may also face the burden of the chronic viral hepatitis and cirrhosis.<sup>3,4,9,45</sup> Although the chronic viral hepatitis is unlikely to be associated with OS, the severity of cirrhosis is an important prognostic factor for HCC patients' OS. Child-Pugh score is the most common tool for grading cirrhosis in clinical practice.<sup>46</sup> In this study, Child-Pugh score was shown as a strong independent prognostic factor for survival outcome, which was confirmed by

**Table 3.** Cox regression analysis of HCC OS by PS, Child-Pugh score, PVT, BCLC stage, and primary treatment modalities.

	B	SE	WALD	DF	SIGNIFICANCE	EXP(B)	95% CI FOR EXP(B)	
							LOWER	UPPER
PS	0.511	0.087	34.333	1	<.001	1.7	1.4	2.0
Child-Pugh score	0.116	0.034	11.415	1	.001	1.1	1.0	1.2
PVT	0.151	0.117	1.669	1	.196	1.2	0.9	1.5
BCLC stage	0.420	0.076	30.947	1	<.001	1.5	1.3	1.8
Primary treatment modalities	0.006	0.024	0.071	1	.790	1.0	0.9	1.1

Abbreviations: BCLC, Barcelona Clinic of Liver Cancer; CI, confidence interval; HCC, hepatocellular carcinoma; OS, overall survival; PS, performance status; PVT, portal vein thrombus.

**Table 4.** Distribution of POD (hospital/home) according to patients' residences (urban area/rural area).

PATIENT'S RESIDENCE	PLACE OF DEATH		TOTAL	
	HOME	HOSPITAL		
Rural area				<i>P</i> = .007 OR [95%CI] = 2.05 [1.21-3.47]
N	292	48	111	
%	85.9%	14.1%	100.0%	
Urban area				
N	83	28	340	
%	74.8%	25.2%	100.0%	
Total				
N	375	76	451	
%	83.1%	16.9%	100.0%	

Abbreviations: CI, confidence interval; OR, odds ratio; POD, place of death.

the Cox regression analysis adjusted by PS, PVT, BCLC stage, and primary treatment modalities. With the hazard ratio of 1.1, the OS was proved to be negatively related to the Child-Pugh score. This result of the study is consistent with those of large studies in Asia, Europe, and Australia.<sup>3,4,28,47</sup>

Staging is one of the key steps to make treatment decision and prognosis of HCC. Currently, there is no consensus on staging system and treatment guidelines for HCC. The BCLC staging system is the most commonly used, because its assessment is based on the tumor status, the degree of cirrhosis, and the patient's PS.<sup>48</sup> Studies in different countries have confirmed the important prognostic value of BCLC staging, the higher the BCLC stage is, the shorter the survival time is.<sup>3,5,35,49</sup> The BCLC prognostic value was also shown clearly in this study with the estimated median survival of BCLC stage A2, B, C, and D was 38.0, 13.5, 4.0, and 1.0 months, respectively ( $P < .001$ ). The median OS of HCC patients with advanced/end-stage disease ranged from 1 to 4 months.

The sex disparity in HCC survival outcome was well documented before, whereby females' survival outcome was

significantly better than that of males.<sup>50,51</sup> In this study, OS in the female HCC patient group was higher than that of the male group, but the difference was not statistically significant. There could be some reasons for this. First, females' several biological factors such as genetic factors and hormonal factors have been proved to help inhibit the development of HCC.<sup>52,53</sup> Second, males are more likely to expose to harmful behavioral factors such as smoking and/or alcohol abuse that may have negative effects on the prognosis of HCC.<sup>53</sup> In this study, most of HCC patients lived in Hanoi, where the rate of both smoking and drinking in men is nearly 30 times higher than in women.<sup>54</sup> However, the number of female HCC patients in this study was relatively low (88 of 674 patients) that may not represent the female HCC patients in community in Hanoi as well as in Vietnam.

Regarding the initial treatment modality, in this study, it was strongly and negatively associated with OS ( $P < .001$ ) in univariate analysis by the log-rank test. However, it appeared not an independent prognostic factor for OS in the multivariate analysis adjusted for PS, Child-Pugh score, and BCLC stage using the Cox model. This result may attribute to the fact that

most HCC patients in this study was at advanced stage, when the role of the initial treatment modality was no longer prominent, especially with curative treatment such as surgery, RFA.

### *End-of-life care and place of death*

In this study, at the time of initial diagnosis, only 31.1% of HCC patients were diagnosed at the early stage (BCLC stage 0, A), which spares the chance for curative treatment, whereas 68.9% of HCC patients were diagnosed at an incurable stage (BCLC stage B was 24.5%, stage C or D was 44.1%), when the treatment purpose was only to relieve symptoms and prolong survival.

High rate of late diagnosis and difficulty in accessing targeted drugs were probably the main reasons for the modest OS time of 10.0 months for all stage of HCC patients in this study. Remarkably, the rate of HCC patients with newly diagnosis at advanced/end stage (BCLC stage C, D) was up to 44.1% with the median survival time ranging from 1 to 4 months. Therefore, the need of hospice care for HCC patients is very high. In addition, 83.1% of HCC patients in this study died at home, which posed the crucial need of home-based hospice care service for HCC patients in Vietnam.

When comparing the POD situation in this study with other studies in Nilsson's systematic review, we found a rather wide difference, as the rate of died-at-home among cancer patients in Nilsson et al's<sup>55</sup> study was only 40.4%, less than a half of that of this study (83.1%). There may be some reasons for this difference and for high rate of dying at home among cancer patients in Vietnam. First, culturally, family value is highly important in Vietnam; thus, most patients want to die at home, their life-long familiar place surrounded by their loved ones.<sup>56</sup> Second, economically, hospital expenses, even with insurance covering, are still too high for long-term in-patients, especially those from the rural area, because of their limited affordability and difficulty in accessing cancer centers in the city, which may cost them more on transportation, accommodation, and other expenses for their caregivers who are their family members. Last but not least, there is the norm that staying in hospital at the end-stage is wasteful because the disease is incurable; therefore, patients and their family would rather save money to use for other family members or purposes. Consequently, many cancer patients spent their end-of-life time at home in suffering due to lack of proper medical and palliative care.

This study results also showed that HCC patients living in the rural area had significantly higher rate of dying at home than those living in the urban area with OR [95% CI]=2.05 [1.21-3.47]. This is a challenge for health care providers in Vietnam such as our hospital to deliver home-based hospice care service, as the capacity and infrastructure at the grassroots level of the health system in rural areas are still limited.

### *Study limitations*

We are aware that this study has limitations. First, this is a retrospective descriptive study with modest sample and convenient

sampling; therefore, the representative value is not very high. Second, some factors that may be related to the survival outcome were not addressed in this study, including comorbidities, viral hepatitis treatment, tumor location, number of tumors, PVT grade, and subsequent treatment modalities (after primary treatment), because they were not sufficiently recorded in the medical records. Third, information on the patients' date of death collected through interviewing with relatives (by phone, postal mail or email) may not be accurate in some cases due to the error of recall. Finally, although this is the first study in Vietnam that addressed POD among cancer patients, patients' preferred POD and its related factors were not yet investigated.

### **Conclusions**

Hepatocellular carcinoma is a poor-prognosis disease with a modest median OS of 10.0 months of all stages. Survival outcome-related factors include PS, PVT, Child-Pugh score, BCLC staging, and primary treatment modalities. The prognostic factors for HCC OS were PS, Child-Pugh score, and BCLC stage. Relating the actual POD of HCC patients, 83.1% of them died at home, and patients living in the rural area were more likely to die at home than patients living in the urban area suggested that home-based hospice care is a crucial need and should be paid more attention, especially in the rural area.

From these findings, it is recommended that cancer patients at advanced stage and their families should be informed comprehensively about the prognosis and available service options for end-of-life care. In addition to management of physical symptoms, it is necessary to provide psychological and social support for advanced cancer patients appropriately. Remote counseling support should be considered for cancer patients if their preferred POD is home, especially in case home-based hospice care is not yet available or not affordable. Most importantly, it is necessary to have a legal framework as well as official guidelines in Vietnam to facilitate the health care providers in distant and/or home-based palliative and hospice care service operation.

Further studies are recommended to:

- Address more factors that could be potentially prognostic factors for HCC patients' survival outcome.
- Survey the HCC patients' preferred POD and related factors.
- Conduct further studies examining barriers to home-based palliative and hospice care service, especially in the rural area.

Further studies should be in a larger scale and designed as observational, multicentered, and data should be collected from all levels of the medical referral system. In addition, the combination of qualitative and quantitative approaches should be used to acquire more comprehensive and in-depth data.



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## Author Contributions

Dr DCL was in charge of developing conception, study design and execution, data interpretation, drafting and revising the manuscript, and corresponding with the publisher. Dr TMN and Dr DHN were in charge of data acquisition and analysis. Dr DTN was in charge of critically reviewing the manuscript. Dr LTMN was in charge of reviewing and approving the version to be submitted and published.

## Ethics Approval and Informed Consent

The study was approved by the Scientific Council and Medical Ethics Committee of Hanoi Oncology Hospital, Vietnam by Decision of approval no. 885/QĐ-BVUB on April 26, 2021. Information on both survival time and POD were consented and provided by patient's next of kin.

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