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Survival Rate of Hepatocellular Carcinoma Patients with Varying Individual Characteristics: A Retrospective Cohort Study

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ABSTRACT

Background: There is a continuous demand for an integrated survival analysis that takes into account clinical biomarkers and socio-demographic factors in Hepatocellular carcinoma (HCC) patients from Southeast Asia. This study figured out the mortality predictors that were independent of HCC patients at a major tertiary referral center in Indonesia.

Methods: This retrospective cohort study looked into 123 HCC patients who were admitted to Dr. M. Djamil General Hospital, Padang (2018-2023). These patients were selected by simple random sampling. Survival analysis was conducted using Kaplan-Meier curves, log-rank tests, and multivariate Cox regression.

Results: Median survival was 284 days with mortality at 24.4%. Univariate analysis showed that albumin <3.5 g/dL (HR=7.67, p=0.045), AFP ≥20 ng/mL (HR=2.16, p=0.044), age ≥59 years (HR=2.38, p=0.018), and obesity (HR=3.43, p=0.013) were significantly associated factors. Multivariate Cox regression indicated that AFP level was the leading factor (adjusted HR=3.94, 95%CI: 1.67-9.33, p=0.002), followed by age ≥59 years (adjusted HR=3.52, p=0.002) and education (adjusted HR=0.36, p=0.014).

Conclusions: AFP level, old age, and education were the independent factors of HCC deaths in Central Sumatra. Besides, the conjunction of clinical and socio-demographic factors may be utilized for prognostic risk stratification to pinpoint the most at-risk groups and hence direct the targeted interventions that are most compatible with resource-limited settings predominately HBV-related HCC.

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Introduction

Hepatocellular carcinoma (HCC) is still a significant global health problem and, as such, it is ranked as the sixth most frequently diagnosed cancer and the third major cause of cancer-related deaths globally (Sung et al., 2021). GLOBOCAN reported liver cancer to be the source of nearly 906,000 new cases and 830,000 deaths in 2020, and the forecasts point to a 56.4% increase in new cases and a 55.7% increase in death rates by 2040 (Global Cancer Observatory, 2024; Rumgay et al., 2022). HCC is the fourth most common cancer in Indonesia. It is estimated that there were 21,392 new cases (5.4% of the total cancer burden) and 20,920 deaths in 2020 (Global Cancer Observatory, 2022). The case fatality rate, which is the ratio of deaths to new cases, is very high and thus Llovet et al. (2021) point out that it not only reflects the severe nature of HCC but also underlines the urgent necessity of enhancing prognostic stratification as a means of guiding clinical decision-making.

In hepatocellular carcinoma prognostication recent advances have led to identification of several clinical biomarkers that can be used as independent survival predictors, among which alpha-fetoprotein (AFP) and albumin levels are the most powerful indicators. A number of studies have reported elevated AFP levels (≥20 ng/mL) to be correlated with increased tumor burden, greater incidence of vascular invasion, and shorter survival in various cohorts(Hao et al., 2021; Tangkijvanich et al., 2022). The research that involved multiple centers by Hao et al. (2021) found out that patients who had AFP ≥20 ng/mL were more than twice as likely to die (HR=2.015, 95%CI: 1.45-2.80, p<0.001) as those with lower levels, thus pointing to the dual role of AFP as a diagnostic and prognostic marker. Also, albumin shortage (<3.5 g/dL) has been identified as a sign of hepatic functional reserve and systemic inflammation. Carr and Guerra (2023) found that HCC patients with albumin ≤3.5 g/dL had significantly shorter survival (HR=2.28, 95%CI: 1.65-3.15, p<0.001) and this was attributed to the vicious cycle of liver dysfunction, malnutrition, and cancer progression (Johnson et al., 2019). However, the extent to which clinical biomarkers and patient-level characteristics contribute to the condition in medical facilities with limited resources is still not clear.

In addition to clinical biomarkers, there is emerging research that sociodemographic factors significantly influence HCC survival patterns though studies show differences from one population to another (Petrick et al., 2020). Age has been counted among non-modifiable risk factors and old age (≥60 years) has been linked with shorter survival most probably due to lesser physiological reserve, more comorbidities, and poor tolerance to the heavy therapies (Chen et al., 2022; Liang et al., 2021). Chen et al. (2022) through a population-based study, showed that people aged ≥59 years had a 1.415 times higher death risk than the younger ones which indicates that prognostic heterogeneity depends on age. Similarly, the matter of obesity has been raised in the same terms as a modifiable risk factor whereby metabolic syndrome-related HCC has been shown to have different biological and clinical features (Younossi et al., 2023). Zhou et al. (2023) found obesity to be a factor that increased the risk of HCC by 1.62 times in the Multiethnic Cohort and this was explained as a result of the development of NAFLD and chronic systemic inflammation. Nevertheless, survival after diagnosis of obesity remains a source of debate with the cause of contradictory studies results in etiology and treatment modality (Singal et al., 2022). Socioeconomic factors such as marital status and educational attainment have also been suggested to be the causes of survival gaps and this is presumed to be due to differences in the access to care, adherence to the treatment, and psychosocial support (Lee et al., 2020; Zheng et al., 2021). On the other hand, most of these research works are done in wealthy Western or East Asian countries and hence their results cannot be applied to Southeast Asian where the healthcare system, disease, and patient demographics are different.

In spite of the increasing number of publications concerning the HCC prognostic factors, a lot of vital questions about Southeast Asian populations remain unanswered. The majority of survival studies have been performed in countries with good healthcare systems (United States, Europe, Japan, South Korea) where there are programs for early detection, multidisciplinary tumor boards, and easy access to curative treatments (resection, transplantation, ablation). On the contrary, patients in Indonesia mostly come at the stage of the disease when it is already advanced because of the lack of surveillance infrastructure and late diagnosis, thus very different from the prognostic landscape (Bachtiar et al., 2022). Moreover, the main cause of HCC in Indonesia is hepatitis B virus (HBV), whereas the trend in the West is toward the rise of NAFLD-associated HCC (Huang et al., 2022). This difference in etiology may lead to the change of the relative importance of the clinical and sociodemographic prognostic factors and yet we know very little from Indonesia about it. The regions of Central Sumatra, in particular, have been experiencing a significant increase in the number of HCC cases with Dr. M. Djamil General Hospital, the main referral center, reporting growth from 79 cases in 2018 to 134 in 2023 (RSUP Dr. M. Djamil Report Team, 2023). Such a rise of 70% in five years calls for a survival determinants study that would not only shed light on this issue but also help local prevention and treatment strategies. Finally, while individual studies have investigated clinical biomarkers or

sociodemographic factors separately, there is no comprehensive analysis that combines both domains in a single Indonesian cohort.

To bridge these gaps, this work offers the first in-depth survival study of HCC patients in Central Sumatra. It looks at the independent as well as the combined impact of clinical biomarkers and sociodemographic attributes on the risk of mortality. This retrospective cohort study is mainly concerned with: (1) establishing HCC patients' median survival time and survival probability in a major tertiary referral hospital in Padang; (2) exploring the link between clinical factors (albumin level, AFP level, comorbidities) and survival outcomes; (3) determining the effect of sociodemographic characteristics (age, sex, obesity status, marital status, education level) on HCC prognosis; and (4) using multivariate Cox regression analysis to find out the most dominant independent predictors of mortality. This project, by merging clinical and sociodemographic aspects within a single analytical framework, intends to create a detailed prognostic profile for the Central Sumatran population thereby aiding risk stratification, treatment delegation, and healthcare resource allocation in resource-limited settings. In addition, these outcomes may be instrumental in developing the regionally tailored prognostic models which take into account the unique epidemiological and healthcare scenarios of Southeast Asia.

Method

Study Design and Setting: The retrospective cohort study of patients with hepatocellular carcinoma was held at Dr. M. Djamil General Hospital RSUP Dr. M. Djamil, 1000-bed tertiary referral center, and a teaching hospital in Padang City, West Sumatra Province, Indonesia. As the major referral hospital for Central Sumatra, RSUP Dr. M. Djamil had served a catchment population of approximately 5.5 million across eight provinces and provided comprehensive oncology services, including medical oncology, radiation therapy, and multidisciplinary cancer care. The study made use of medical records of inpatients from January 1, 2018, to December 31, 2023, with follow-up data collected until June 30, 2024, thus allowing for a minimum follow-up period of six months for all the patients involved in the study.

Study Population and Eligibility Criteria: A patient was considered eligible for inclusion in the study if he/she was 18 years of age or older at the time of hepatocellular carcinoma diagnosis and had a confirmed diagnosis of hepatocellular carcinoma which was based on at least one of the following evidence: biopsy or surgical specimen histopathology; imaging conforming to AASLD criteria that comprise arterial phase hyperenhancement and portal venous or delayed phase washout on dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with lesion size greater than 1 cm ; or AFP level combined with imaging results in cirrhosis AFP > 200 ng/mL (Singal et al., 2023). Moreover, the inclusion criteria further required that the patients had primary hepatocellular carcinoma rather than metastatic disease from other organs, were admitted as inpatients at RSUP Dr. M. Djamil during the study period, and had complete medical records including baseline demographic data, clinical characteristics, laboratory results, and outcome information.

Exclusion criteria for patients were secondary malignancies of the liver or metastatic cancer of the liver from extrahepatic primary sites, mixed hepatocellular-cholangiocarcinoma or pure cholangiocarcinoma, incomplete baseline data making survival analysis impossible such as missing date of diagnosis, outcome status, or follow-up data, prior hepatocellular carcinoma diagnosis or treatment before the study period to permit only incident cases analysis, and unfollowed patients within 30 days of diagnosis without a documented outcome.

Sample Size Determination: The sample size was determined by a formula for survival analysis in Cox regression models introduced by Schoenfeld (1983). The calculation considerations were: two-sided significance level 0.05, power 80%, proportion of exposed and unexposed groups 0.5 each, expected hazard ratio 2.0 based on previous literature and event rate 30%. According to these points there was a need for a minimum of 110 patients. Taking into consideration about 10% of possible missing data, the minimum number of patients to be recruited was 120 so as to have enough statistical power for the planned analyses.

Sampling Procedure: Simple random sampling method was used to select eligible patients from the sampling frame. The sampling process started with the identification of medical records of patients with ICD-10 codes C22.0, which stands for liver cell carcinoma, and C22.9 representing malignant neoplasm of the liver unspecified from 2018 to 2023 in the hospital electronic database. As a result, there were 431 potential cases at the initial stage. Next, these medical records were screened for eligibility based on the inclusion and exclusion criteria, thus 187 patients met the criteria. Each eligible medical record was given a unique ID number, and a computer-generated random number sequence using R software version 4.3.1 was applied to randomly select 123 patients for the final study

cohort. After that, the selected medical records were brought from the medical records department and thoroughly examined for data collection.

There were 244 patients who were left out for several reasons during the selection process. The reasons behind the 244 patients' exclusion were that 52 of them had secondary malignancy, 31 had cholangiocarcinoma, 89 had incomplete medical records, 28 had previous HCC diagnosis or treatment, and 44 patients were lost to follow-up within 30 days of diagnosis. The study's final population included 123 patients, 93 of whom were censored (75.6%) while 30 patients died (24.4%) during the observation period. The detailed study flowchart which is in line with STROBE guidelines was prepared to explain the patient selection process and exclude the reasons at each stage.

Statistical Analysis Methods: All statistical analyses in this research were performed using SPSS version 26.0 from IBM Corporation, Armonk, New York, USA, and R software version 4.3.1 from the R Foundation for Statistical Computing, Vienna, Austria. For hypothesis testing, a two-sided p-value less than 0.05 was considered statistically significant. Descriptive statistics were implemented to the whole set of study variables Continuous variables were presented as mean ± standard deviation if they were normally distributed or median with interquartile range in case distributions were skewed. Normality was checked by the Shapiro-Wilk test. Categorical variables were expressed in numbers and percentages. The main survival measures such as median survival time along with 95% confidence intervals and survival rates at 6 months, 1 year, 2 years, and 3 years were determined for the total cohort.

Sample Size Adequacy Assessment: Post-hoc power analysis was done basing on the first 24.4% event rate and the last sample size of 123 patients. With 30 events recorded, the research reached a statistical power of 82% to demonstrate a hazard ratio of 2.0 or higher for binary predictor variables with a 50% prevalence using a two-sided significance level of 0.05. The present estimation of power confirmed that the study was suitably powered to conduct the primary analyses that examined the association between predictor variables and overall survival.

Ethical Considerations: This study received ethical approval from the Research Ethics Committee of Dr. M. Djamil General Hospital, Padang, under approval number DP.04.03/D.XVI.XI/222/2024. The research was carried out in obedience to the principles laid down in the Declaration of Helsinki and Indonesian national research ethics guidelines. Because this is a retrospective study using secondary data that have been de-identified and extracted from medical records, the ethics committee waived the requirement for informed consent. Patient confidentiality was respected at all stages of the study. Data were completely anonymized prior to analysis, and no individual patient identifiers were included in the research database or any publications resulting from this work. Only authorized medical records staff and research team members who all signed confidentiality agreements had access to identifiable patient information during the data collection phase.

Results and Discussions

Hepatocellular carcinoma (HCC) is one of the primary types of liver cancer with the highest mortality rate among all cancers in Indonesia. Based on a study conducted on patients with HCC during 2018–2019, it was found that 75.5% of patients were censored, while 24.4% experienced events. In addition, the average survival time of HCC patients was 284 days, with the longest survival reaching 619 days and the shortest occurring on the second day, as shown in **Figure 1**.

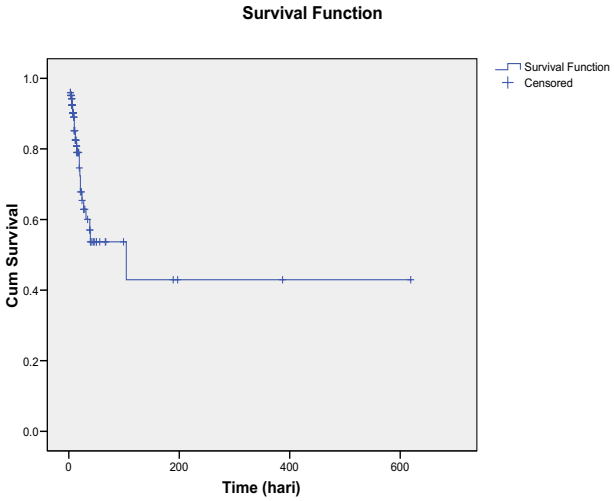

Figure 1. Kaplan–Meier Survival Curve of Hepatocellular Carcinoma Patients at Dr. M. Djamil General Hospital, Padang, 2018–2023.

In the present study, 93 patients (75.8%) were censored, while 30 patients (24.4%) experienced events. Based on patient characteristics, the frequency distribution of HCC patient survival at Dr. M. Djamil Central General Hospital Padang during 2018–2023 showed that most patients had low albumin levels (<3.5 g/dL; 81.3%) compared to those with normal albumin levels (3.5–5.0 g/dL), normal AFP levels (<20 ng/mL; 56.3%) compared to high AFP levels (≥20 ng/mL), were aged <59 years (66.7%), male (86.2%), non-obese (94.3%), had comorbidities (56.9%), were married (87.8%), and had a low education level (53.7%), as presented in **Table 1**.

Table 1. Frequency Distribution of Hepatocellular Carcinoma Patients at Dr. M. Djamil General Hospital, Padang, 2018–2023

Characteristics	Frequency	%
Patient Outcome Status		
Cencored	93	75,6
Event	30	24,4
Albumin Level		
Normal (3,5-5,0 g/dL)	23	18,7
Low (<3,5 g/dL)	100	81,3
AFP Level		
Normal (<20 ng/ml)	70	56,9
High (≥20 ng/ml)	53	43,1
Age		
< 59 tahun	82	66,7
≥ 59 tahun	41	33,3
Gender		
Male	106	86,2
Female	17	13,8
Obesity Status		
No	116	94,3
Yes	7	5,7

Characteristics	Frequency	%
Comorbidity		
No	53	43,1
Yes	70	56,9
Marital Status		
Married	108	87,8
Unmarried/Divorced	15	12,2
Education Level		
High	57	46,3
Low	66	53,7

Based on the analysis, albumin level, AFP level, age, and obesity status were significantly associated with the survival of HCC patients at Dr. M. Djamil Central General Hospital Padang from 2018 to 2023. Meanwhile, sex, comorbidity, marital status, and education level showed no significant association. Furthermore, AFP level was identified as the most dominant risk factor affecting HCC patient survival, as shown in **Table 2**.

Table 2. Analysis Results of Variables Associated with the Survival of Hepatocellular Carcinoma Patients at Dr. M. Djamil General Hospital, Padang, 2018–2023.

Variables	*Cox regression*			*Multivariate cox regression.*		
	p-value	**HR**	**95%CI**	***p-value***	**HR**	**95%CI**
Albumin Level	0,045	7,67	1,04-56,32	-	-	-
AFP Level	0,044	2,16	1,02-4,56	0,002	3,94	1,67-9,33
Age	0,018	2,38	1,16-4,89	0,002	3,52	1,61-7,68
Gender	0,20	1,80	0,73-4,44	-	-	-
Obesity Status	0,013	3,43	1,29-9,05	-	-	-
Comorbidity	0,150	1,78	0,81-3,88	-	-	-
Marital Status	0,079	2,25	0,91-5,54	-	-	-
Education Level	0,154	0,58	0,28-1,23	0,014	0,36	0,17-0,81

The findings showed a significant association between age and HCC survival (p-value = 0.018), indicating that patients aged ≥59 years had a 2.381-fold higher risk of experiencing an event compared to younger patients (<59 years). This finding is consistent with the results of Fangjie Chen et al. (2022), who reported that age significantly affected HCC survival, with a hazard ratio (HR) = 1.415, indicating that patients aged ≥59 years had a 1.415-fold higher risk of death than those aged <59 years. The association between age and HCC survival may be explained by metabolic disturbances and comorbid conditions that progressively impair liver function with advancing age.

In addition to age, obesity was also significantly associated with HCC survival (p-value = 0.013), with obese patients having a 3.462-fold higher risk of experiencing an event compared to non-obese patients. This result is consistent with the findings of Kali Zhou et al. (2023), who also reported a significant association between obesity and HCC survival, with a hazard ratio (HR) = 1.62, indicating that obese patients had a 1.62-fold higher risk of death compared to non-obese patients. Obesity increases the risk of HCC through its association with metabolic syndrome, which can worsen prognosis. Moreover, obesity is frequently associated with non-alcoholic fatty liver disease (NAFLD) or other liver dysfunctions that increase the risk of HCC progression, thereby affecting patient survival. These findings suggest that obesity contributes to poorer survival outcomes among HCC patients.

However, not all individual characteristics showed a significant association with HCC survival. In this study, sex was not significantly associated with patient survival (p-value = 0.20). This finding contrasts with the results of Wei-Lun Liou et al. (2023), who reported that male patients had a 1.19-fold greater risk of death compared with female patients. This discrepancy may be influenced by the age at diagnosis. In the present study, 64.7% of female

patients were diagnosed at ≥59 years of age, when estrogen—a protective hormone—naturally declines. Furthermore, comorbidities may also contribute to survival differences between sexes.

Marital status was not significantly associated with HCC survival (p-value = 0.079). This finding differs from that of Fangjie Chen et al. (2022), who reported that unmarried patients had a 1.389-fold higher risk of death compared with married patients. Similarly, Fangfang Liang et al. (2021) found that widowed or divorced patients had a 1.556-fold higher risk of death. The association between marital status and HCC outcomes may be explained by the social, emotional, and financial support provided by a spouse, which can reduce psychological distress, anxiety, and fear following diagnosis. However, findings from this study suggest that emotional and social support may also be derived from other close family members, such as parents, children, or siblings.

Similarly, education level was not significantly associated with HCC survival (p-value = 0.154). This finding contradicts the results of Rachel M. Lee et al. (2020), who reported that patients with lower education levels had a 1.496-fold higher risk of death compared with those with higher education levels. Education level may influence health literacy and an individual's ability to seek and understand health information, which in turn influences disease awareness and decision-making regarding healthcare utilization and treatment options (Lee et al., 2020; Sarpel et al., 2018). However, findings from this study suggest that individuals with lower education levels may still access health-related information, either independently or through family and community networks.

HCC survival was also influenced by clinical factors, including albumin levels, AFP levels, and comorbidities. Albumin level was significantly associated with survival (p-value = 0.045), with patients having low albumin (<3.5 g/dL) showing a 7.669-fold higher risk of experiencing an event compared with those with normal albumin levels. This finding is consistent with the study by Brian I. Carr and Vito Guerra (2023), who reported a significant association between albumin and HCC survival (HR = 2.28), indicating that patients with albumin ≤3.5 g/dL had a 2.28-fold greater risk of death than those with albumin >3.5 g/dL. Albumin serves as a prognostic biomarker in HCC, where low levels indicate impaired liver function and are associated with poor prognosis and shorter survival.

AFP level was also significantly associated with HCC survival, where patients with high AFP levels (≥20 ng/mL) had a 2.157-fold greater risk of death compared with those with normal AFP levels (<20 ng/mL). This result aligns with the findings of Xiang-Yong Hao et al. (2021), who reported a significant relationship between AFP level and HCC survival (HR = 2.015). AFP is a well-established prognostic marker for HCC and correlates with tumor size and extent. Elevated AFP levels generally reflect larger or more aggressive tumors, as tumor cells produce higher levels of AFP (Ekinci et al., 2018; Hao et al., 2021). Therefore, high AFP levels are often associated with a heavier tumor burden and poorer prognosis.

However, comorbidity was not significantly associated with HCC survival (p-value = 0.150). This finding differs from that of Kanokwan Pinyopornpanish et al. (2022), who reported that HCC patients with cirrhosis had a 1.45-fold higher risk of death than those without cirrhosis. Comorbid conditions may accelerate hepatic fibrosis and tumor progression, impair liver function, and ultimately reduce survival. However, findings from this study suggest that non–liver-related comorbidities may also influence survival outcomes among HCC patients.

Multivariate Cox regression analysis revealed that AFP level, age, and education level were significantly associated with the survival of HCC patients. This analysis adjusted for all variables in the model to assess the independent effect of each. Moreover, AFP level emerged as the most influential factor affecting HCC survival (HR = 3.942), indicating that patients with elevated AFP levels had a 3.942-fold greater risk of death compared with those with normal levels. This finding suggests that AFP level serves not only as a diagnostic marker but also as an important prognostic indicator. Based on this study's findings, individual characteristics including age, obesity status, albumin level, and AFP level were found to influence the survival of patients with hepatocellular carcinoma.

Conclusions

Albumin level, AFP level, age, and obesity status were significantly associated with the survival of hepatocellular carcinoma patients, with AFP level identified as the most dominant factor. These findings suggest that individual characteristics can impact the survival outcomes of patients with hepatocellular carcinoma. The results are expected to provide a deeper understanding of the factors affecting the survival of patients with hepatocellular carcinoma and serve as a foundation for future studies to develop broader insights into survival-related determinants in these patients. Moreover, these findings are anticipated to contribute to more informed decision-making in disease prevention and management efforts, particularly among healthcare practitioners and related stakeholders, thereby helping to reduce mortality rates associated with hepatocellular carcinoma.

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