

## Clinical Manifestations and Laboratory Examination Findings of Hepatocellular Carcinoma at A Tertiary Care Facility in Bandung: An Annual Observation Study

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### Abstract

**Background:** Hepatocellular Carcinoma (HCC) is the most prevalent liver cancer with high mortality. Early detection is important for better patient outcomes. The aim of this study was to explore clinical manifestations and laboratory examinations among HCC patients in a tertiary care facility.

**Methods:** This was a cross-sectional descriptive study with a total sampling method, reviewing the medical records of patients with HCC in the Outpatient Clinic of Dr. Hasan Sadikin General Hospital between January and December 2019. Clinical manifestations, laboratory findings, and imaging results data were collected.

**Results:** Of the 112 HCC patients included in this study, the HCC findings among new patients at the Outpatient Clinic were 8.4%, with hepatitis B (80.8%) as the major etiology. Complaints of abdominal pain (65.2%) were frequent. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated in 90.6% and 67% of patients, and total bilirubin levels were increased in 58.8% of patients. In contrast, hemoglobin and albumin levels decreased in 56.2% and 78.1% of patients, respectively. The characteristics of tumor were mainly multinodular, with a size of 3–10 cm.

**Conclusions:** The annual proportion of HCC at Dr. Hasan Sadikin General Hospital in 2019 is 8.4% among all outpatient gastrointestinal and hepatology cases, with hepatitis B as the most common etiology. Abdominal pain is the predominantly prevalent clinical manifestation with elevated ALT and AST levels.

**Keywords:** Clinical manifestation, hepatocellular carcinoma, supporting examination

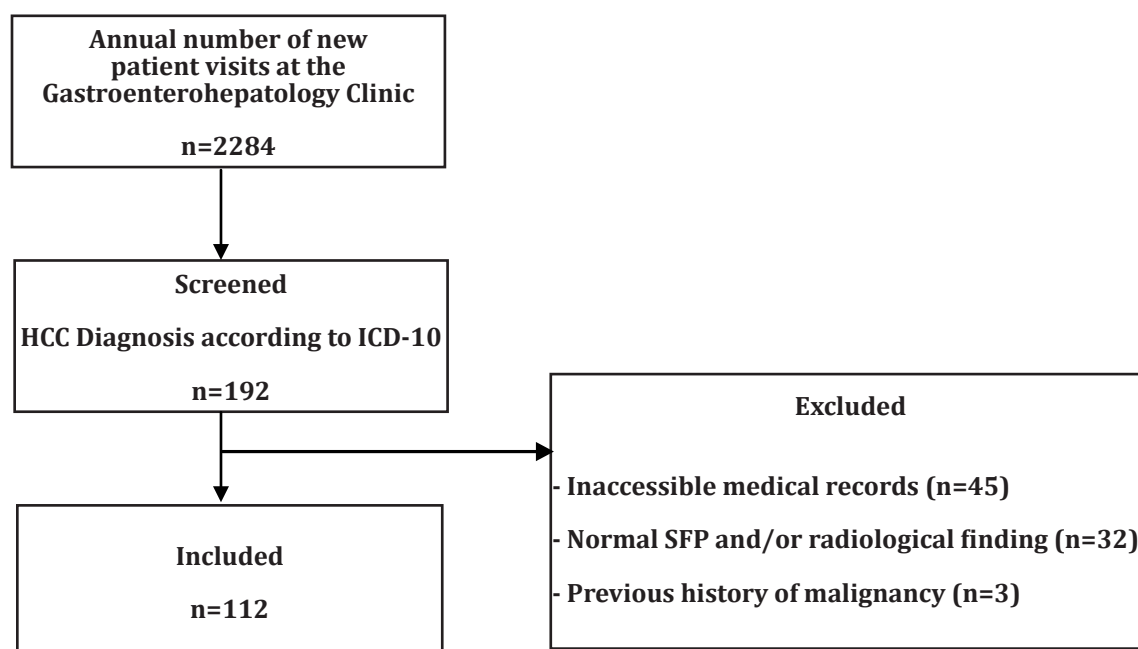
### Introduction

Hepatocellular carcinoma (HCC) is one of the primary liver malignancies originating from liver parenchymal cells,<sup>1</sup> HCC is caused by chronic liver fibrosis due to viral infection (hepatitis B or C virus) or metabolic disorders (fatty liver and excessive alcohol consumption). The presence of HCC is often unidentified unless signs and symptoms appear due to the tumor size or the advanced stage of the disease.<sup>2</sup> The Barcelona Clinic Liver Cancer (BCLC) guideline has been currently used to diagnose and manage HCC.<sup>3</sup> Upon entering the symptomatic stage, clinical manifestations

are similar to those of cirrhosis with pain originating in the right upper abdomen that may spread to the shoulder, followed by weight loss and hepatomegaly.<sup>4</sup>

Liver cancer is the sixth most common cancer globally and the fourth rank of cancer mortality. HCC contributes to approximately 75 to 85% of liver cancer cases.<sup>5</sup> In Indonesia, liver cancer ranks fourth as the most common cancer and mortality due to cancer.<sup>6</sup> According to the Indonesian Association for the Study of the Liver (*Perhimpunan Peneliti Hati Indonesia*, PPHI), the incidence of HCC in Indonesia is 13.4 per 100,000 population age-standardized rate (ASR).<sup>7</sup>

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**Figure 1 Study Flowchart**

The previous report has shown that the prevalence of hepatitis B virus (HBV) in Indonesia is 7.1%, classified as intermediate to high endemicity.<sup>8</sup> The prevalence of HBV among HCC patients is estimated to be 37–68%, leading to the most common etiology of HCC.<sup>9</sup> Moreover, clinical manifestations and laboratory results among this disease are still unclear, leading to high mortality. Therefore, the aim of this study was to explore the clinical manifestations and laboratory examinations among HCC patients in tertiary care facilities, Dr. Hasan Sadikin General Hospital, Bandung. This finding will help the clinicians to make an early diagnosis for a better prognosis.

## Methods

This was a cross-sectional descriptive study conducted between October and November 2020. Data were taken from the medical records of outpatients with a diagnosis of HCC, according to the ICD-10 code at Dr. Hasan Sadikin General Hospital from January to December 2019. Inclusion criteria were newly diagnosed HCC patients with AFP levels of  $\geq 400$  ng/ml, or radiological findings concluded as HCC.<sup>10</sup> Exclusion criteria were patients with a history of other malignancies, liver metastatic malignancies, and medical records that were not accessible during the study period.

Data on patients diagnosed with HCC were accessed using ICD-10 codes C.22 for

“Malignant neoplasm of liver and intrahepatic bile ducts” and C.22.0 for “Liver cell carcinoma”. This study has received permission from the Research Ethics Committee of the Universitas Padjadjaran No. 633/UN6.KEP/EC/2020 dated July 20, 2020, and Research Permit issued by Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung No. LB.02.0/X.2.2.1/19549/2020.

Data were summarized using an electronic worksheet, Microsoft® Excel 2016, and processed using IBM® SPSS® version 25. The results were presented in tables and figures to show the characteristics of HCC patients, clinical manifestations, and laboratory examinations profiles in numbers and percentages.

## Results

During observation, the proportion of HCC in this study was 8.4% (192 of 2284 patients). Nevertheless, only 112 subjects were included in this study for further analysis as shown in Figure 1. The median age at diagnosis was 53 years with an interquartile range of 61–46 years, predominantly in males (73.2%). A total of 59 of 112 subjects had a history of hepatitis B as the underlying cause of HCC. The presence of multinodular mass was 85.7% (24 of 28 data collected). From the 35 data retrieved, the size of nodule ranged from 3–10 cm (54.3%), followed by nodules >10 cm (40%) (Table 1).

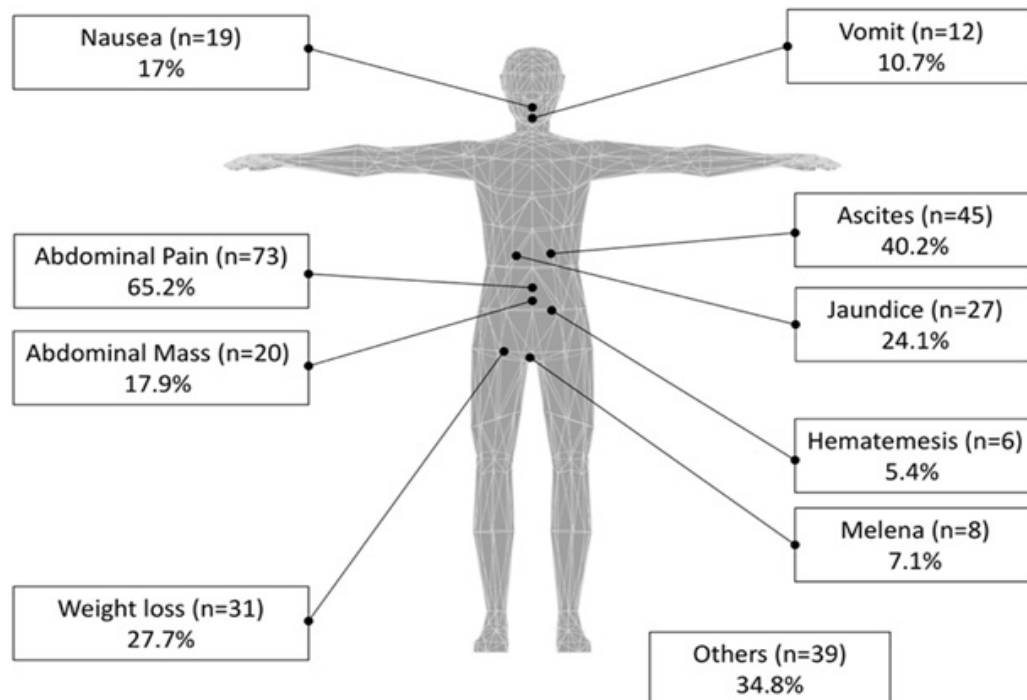
**Table 1 Characteristics of Patient with Hepatocellular Carcinoma**

Variable	Hepatocellular Carcinoma (n=112)	
	n	%
Age (years)	53.5(61-46)	
Median (IQR) <sup>a</sup>		
Gender		
Male	82	73.2
Female	30	26.8
Etiology <sup>b</sup>		
Hepatitis B	59	80.8
Hepatitis C	9	12.3
Non-Hepatitis	5	6.9
Tumor Nodule <sup>c</sup>		
Singular	4	14.3
Multinodular	24	85.7
The largest nodule size (cm) <sup>c</sup>		
<3	2	5.7
3-10	19	54.3
>10	14	40

Note: <sup>a</sup>=IQR: interquartile range, <sup>b</sup>=Of those reporting etiology and clinical classification, <sup>c</sup>=Of those reporting diagnostic imaging

There were variation in clinical manifestation observed among patients with HCC, the most common being abdominal pain (65.2%), ascites (40.2%), and weight loss (27.7%) (Figure 2). Laboratory examination

findings in HCC subjects were characterized by decreased serum albumin and hemoglobin levels, increased ALT and AST levels, and total serum bilirubin.



**Figure 2 Clinical Manifestations of Hepatocellular Carcinoma**

**Table 2 Laboratory Examination Results of Hepatocellular Carcinoma Patients**

Variable	n	Result Interpretation					
		Decrease		Normal		Elevated	
		n	%	n	%	n	%
<b>Hematology Test</b>							
Hemoglobin	112	63	56.2	46	41.1	3	2.7
Leukocyte	112	6	5.4	58	51.8	48	42.8
Thrombocyte	112	22	19.6	70	62.5	20	17.9
<b>Liver Function Test</b>							
ALT	103	-	-	34	33.0	69	67.0
AST	106	-	-	10	9.4	96	90.6
Bilirubin	102	-	-	42	41.2	60	58.8
Albumin	105	82	78.1	23	21.9	-	-
<b>Coagulation Test</b>							
Prothrombin Time	103	-	-	56	54.4	47	45.6

Note: ALT=alanine aminotransferase; AST=aspartate aminotransferase; n=number of HCC patients being tested; (-)=no data or interpretation available

## Discussion

Hepatocellular carcinoma (HCC) is a liver malignancy originating from hepatocytes and is the most common primary liver malignancy, followed by intrahepatic cholangiocarcinoma.<sup>5</sup> Patients with HCC tend to be diagnosed at an advanced stage, and treatment is challenging at this stage. In contrast, patients with HCC in the early stage usually do not show abnormalities, both clinical manifestations and liver function. Therefore, the diagnosis of HCC is generally delayed until it reaches an advanced stage.<sup>2</sup> The clinical presentation may vary among others; dull abdominal pain in the right upper quadrant spreading to the shoulder, weight loss, and hepatomegaly. Clinical manifestations of HCC patients with cirrhosis generally shows hepatic encephalopathy, ascites, and jaundice.<sup>4</sup> However, in HCC patients without a history of cirrhosis, the clinical manifestations are usually similar to the classic tumor signs and symptoms, i.e., anorexia, malaise, weakness, weight loss,<sup>11</sup> which is consistent with the findings of our study.

Our study shows that HCC is predominantly found in males, with a male-to-female ratio of 2.7:1 and median age of 53 years. This finding is similar to previous studies reported in different countries or continents, which indicates HCC as a global problem worldwide.<sup>12,13</sup> In general, the prevalence of hepatitis B in Indonesia is higher than other hepatitis infections and hepatitis B is the most common etiology of HCC, as previously reported.<sup>9,14</sup> Furthermore, the most common symptom in HCC patients in our study was abdominal pain, consistent with

the study from Saudi Arabia.<sup>12</sup>

Structural damage to the liver interferes with various physiological processes in the body. One of them is the leakage of aminotransferase enzymes produced in the liver into the bloodstream, characterized by elevated liver enzymes in most patients such as AST and ALT levels, similar to studies from the United States.<sup>15</sup> In this study, hematological examination showed that most of the patients had decreased hemoglobin levels. The liver is also an organ that plays a role in storing iron. Liver damage causes iron depletion, which leads to anemia. Moreover, gastrointestinal bleeding due to portal hypertension also contributes to decreased hemoglobin levels, which can be exacerbated by impaired coagulation factors produced by the liver.<sup>16</sup>

There was an increase in bilirubin levels in most of patients, similar to the study from Saudi Arabia.<sup>12</sup> Damage to hepatocytes also results in impaired bilirubin metabolism which increases intrahepatic hyperbilirubinemia.<sup>17</sup> Patients with liver damage have impaired albumin synthesis. Decreased albumin levels can also be caused by the diluting effects of water and salt retention, accumulation of protein in ascites fluid and extracellular space.<sup>18</sup> Albumin levels in this study were found to be decreased in most patients, which is consistent with finding from the United States.<sup>13</sup>

In this study, most of the patients had multinodular tumors. However, a study in Jakarta resulted that singular nodules were more common than multiple.<sup>14</sup> The size of the most common nodules ranged from 3 to 10

cm, followed by large nodules with size >10 cm. This is similar to a previous report, which showed that nodules >3 cm in size tend to be more common than nodules measuring <3 cm.<sup>14</sup> Treatment options for multinodular HCC patients are quite challenging because based on BCLC staging, it could be categorized as intermediate stage. The patient's liver function is a crucial factor in determining whether the patient is still eligible for resection, which was not as successful as the earlier stages. Palliative procedures such as trans-arterial chemoembolization (TACE) or transplantation may be employed.<sup>3,19</sup> Moreover, patients with larger tumor sizes at the time of diagnosis also have lower overall survival rates.<sup>20</sup>

This study has several limitations. First, we conducted retrospective data collection because the data in the medical records were limited or incomplete. As previously described, the diagnosis of HCC is a challenge, particularly in the early stage, where clinical manifestations or laboratory examinations still do not show remarkable findings. Second, we were unable to retrieve the occurrence time of clinical manifestation, which may contribute to the different stages of HCC. Third, although we screened and observed the diagnosis of HCC through the ICD-10 code, there may be a potential bias from the population, in which patients with HCC as a secondary diagnosis and are not included in the ICD-10 code.

To conclude, the proportion of HCC in our study is 8.4% among the total annual gastrointestinal and hepatology cases visiting the outpatient clinic at Dr. Hasan Sadikin General Hospital, with hepatitis B as the most common etiology. The most frequent clinical manifestation is abdominal pain, followed by ascites. Radiological findings are characteristic of a multinodular liver mass. Increased levels of ALT and AST can help identify the occurrence of HCC. These findings may contribute to better diagnosis and management of patient, especially in the early stage of HCC.

## References

1. Sia D, Villanueva A, Friedman SL, Llovet JM. Liver cancer cell of origin, molecular class, and effects on patient prognosis. *Gastroenterology*. 2017;152(4):745–61.
2. Dimitroulis D, Damaskos C, Valsami S, Davakis S, Garmpis N, Spartalis E, et al. From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world. *World J Gastroenterol*. 2017;23(29):5282–94.
3. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology*. 2016;150(4):835–53.
4. Carr BI, editor. *Hepatocellular carcinoma: diagnosis and treatment*. 3<sup>rd</sup> ed. Switzerland: Springer International Publishing; 2016.
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
6. International Agency for Research on Cancer (IARC). *Indonesia-Globocan 2020*. [cited 2021 February 5]. Available from: <https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf>
7. Hasan I, Loho IM, editors. *Konsensus nasional penatalaksanaan karsinoma sel hati*. Jakarta: Perhimpunan Peneliti Hati Indonesia; 2017.
8. Yano Y, Utsumi T, Lusida MI, Hayashi Y. Hepatitis B virus infection in Indonesia. *World J Gastroenterol*. 2015;21(38):10714–20.
9. Muljono DH. Epidemiology of hepatitis B and C in Republic of Indonesia. *Euroasian J Hepato-gastroenterol*. 2017;7(1):55–9.
10. Zhang J, Chen G, Zhang P, Zhang J, Li X, Gan D, et al. The threshold of alpha-fetoprotein (AFP) for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *PLoS One*. 2020;15(2):e0228857.
11. Singal AG, Marrero JA. Hepatocellular Carcinoma. In: Podolsky DK, Camilleri M, Fitz JG, Kalloo AN, Shanahan F, Wang TC, editors. *Yamada's textbook of gastroenterology Part 4*. 6<sup>th</sup> ed. Hoboken: John Wiley & Sons Ltd; 2016. p. 2146–65.
12. Aljumah AA, Kuriry H, Al-Zunaitan M, Al Ghobain M, Al Muaikael M, Al Olayan A, et al. Clinical presentation, risk factors, and treatment modalities of hepatocellular carcinoma: A single tertiary care center experience. *Gastroenterol Res Pract*. 2016;2016:1989045.
13. Kuftinec GN, Levy R, Kieffer DA, Medici V. Hepatocellular carcinoma and associated clinical features in Latino and Caucasian patients from a single center. *Ann Hepatol*. 2019;18(1):177–86.
14. Loho IM, Hasan I, Rinaldi C, Dewiasty E, Gani RA. Hepatocellular carcinoma in a tertiary referral hospital in Indonesia: lack of improvement of one-year survival rates

- between 1998–1999 and 2013–2014. *Asian Pac J Cancer Prev.* 2016;17(4):2165–70.
15. Wong PY, Xia V, Imagawa DK, Hoefs J, Hu KQ. Clinical presentation of hepatocellular carcinoma (HCC) in Asian-Americans versus non-Asian-Americans. *J Immigr Minor Health.* 2011;13(5):842–8.
  16. Gkamprela E, Deutsch M, Pectasides D. Iron deficiency anemia in chronic liver disease: etiopathogenesis, diagnosis and treatment. *Ann Gastroenterol.* 2017;30(4):405–13.
  17. Subbiah V, West HJ. Jaundice (Hyperbilirubinemia) in cancer. *JAMA Oncol.* 2016;2(8):1103.
  18. Carvalho JR, Machado MV. New insights about albumin and liver disease. *Ann Hepatol.* 2018;17(4):547–60.
  19. Abbasoglu O. Role of liver resection in the management of multinodular hepatocellular carcinoma. *World J Hepatol.* 2015;7(20):2237–40.
  20. Wu G, Wu J, Wang B, Zhu X, Shi X, Ding Y. Importance of tumor size at diagnosis as a prognostic factor for hepatocellular carcinoma survival: A population-based study. *Cancer Manag Res.* 2018;10:4401–10.