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Hepatocellular Carcinoma Situation in Indonesia: A Systematic Review of Clinical Staging and Histological Characteristics at the Time of Diagnosis

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. However, systematic data on HCC characteristics in Indonesia are limited.

Objective: To summarize the body of literature on the characteristics of HCC in Indonesia.

Methods: A comprehensive search was conducted in MEDLINE, ScienceDirect, Scopus, Web of Science, and Google Scholar databases without date restrictions. Clinical studies investigating the characteristics of HCC exclusively in Indonesia were eligible for inclusion. Risk-of-bias assessments were conducted, and results were presented descriptively.

Results: Ten studies comprising 1,389 HCC patients were included. The Barcelona Clinic Liver Cancer (BCLC) staging system, reported in 5 studies, revealed a predominance of intermediate to advanced stages (B and C) at diagnosis. Child-Pugh scores, available for 7 studies, indicated variability in liver function, with Child-Pugh A ranging from 12.0% to 85.7%. Hepatitis B virus (HBV) infection was the primary etiological factor, with prevalence ranging from 53.8% to 84.0%. Hepatitis C virus (HCV) infection was less common (1.0% to 25.21%). Non-viral etiologies represented a substantial proportion, reaching up to 37.4% of cases. The mean age at diagnosis ranged from 52.43 to 63.1 years.

Conclusion: This review highlights the late-stage presentation of HCC in Indonesia, the predominance of HBV as an etiological factor, and a significant burden of non-viral HCC. The findings underscore the need for improved early detection strategies, strengthened HBV prevention efforts, and increased attention to metabolic risk factors. Regional variations in HCC characteristics suggest the need for tailored approaches to HCC management across different parts of Indonesia.

KEYWORDS: hepatocellular carcinoma, BCLC staging, prevalence, Indonesia

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I. INTRODUCTION

Hepatocellular carcinoma (HCC) represents a significant global health challenge, ranking as the sixth most common cancer and the third leading cause of cancer-related mortality worldwide (Sung et al., 2021). The global burden of HCC continues to escalate due to its poor prognosis and limited treatment options, particularly in low- and middle-income countries (Yang et al., 2019). In 2020, there were an estimated 905,677 new cases of liver cancer globally, with HCC accounting for approximately 75-85% of these cases (Batheja et al., 2023).

Indonesia, as the fourth most populous country globally and with a unique demographic and environmental profile, presents a distinct context for HCC research. According to GLOBOCAN 2022 estimates, liver cancer ranks as the fifth most common cancer in Indonesia, with an estimated 23,805 new cases and 23,383 deaths (GLOBOCAN, 2024). The 5-year prevalence rate for liver cancer in Indonesia is reported at 10.9 per 100,000 persons, which, while lower than some neighboring countries, still represents a significant health burden.

The country's high prevalence of chronic hepatitis B infection, estimated at 7.1% in the general population (Muljono, 2017), is a major contributing factor to HCC incidence. Additionally, the increasing prevalence of metabolic syndrome, with rates ranging from 21.66%

(95%CI 20.79–22.55%) across different regions of Indonesia (Herningtyas & Ng, 2019), suggests a potentially growing contribution of non-alcoholic fatty liver disease (NAFLD) to HCC incidence in the country.

Previous studies have highlighted the heterogeneous nature of HCC across different geographical regions. For instance, a systematic review by Kulik and El-Serag (2019) demonstrated significant variations in HCC etiology, with hepatitis B virus (HBV) predominating in East Asia and sub-Saharan Africa, while hepatitis C virus (HCV) was more prevalent in Japan, North America, and Europe (Kulik & El-Serag, 2019). Moreover, a multi-center study by Park et al. (2015) across the Asia-Pacific region revealed disparities in HCC staging at diagnosis, treatment modalities, and overall survival rates among different countries (Park et al., 2015).

Despite the significant burden of HCC in Indonesia, systematic data on the characteristics and epidemiology of HCC in the country remains limited, creating a critical knowledge gap. The lack of comprehensive, nationwide data has hindered the development of targeted screening, prevention, and treatment strategies tailored to the Indonesian population. Therefore, this systematic review aims to summarize the body of literature on the characteristics of HCC in Indonesia, with the ultimate goal of improving HCC prevention, early detection, and management strategies in the country.

II. METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

A. Search Strategy

A comprehensive literature search was performed using the following electronic databases: MEDLINE (PubMed), Scopus, Web of Science, ScienceDirect, and hand-search via Google Scholar. The search was conducted without date restrictions, with the last search performed on June 30th, 2024. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to “hepatocellular carcinoma”, “hepatoma”, and “Indonesia” by using Boolean operators.

B. Eligibility Criteria

Studies were included if they met the following criteria: observational studies (cross-sectional, cohort, or case-control studies) or clinical trials involving patients diagnosed with hepatocellular carcinoma in Indonesia. Eligible studies reported on at least one of the following HCC characteristics: demographic information (age, sex), clinical presentation, tumor characteristics, etiology (HBV, HCV, non-viral causes), liver function (Child-Pugh score), or disease stage (BCLC staging). Only peer-reviewed full-text articles published in English or Indonesian were considered. Studies were excluded if they were case reports, editorials, letters, or review articles; not specific to the Indonesian population; or focused solely on treatment outcomes without reporting on HCC characteristics at the time of diagnosis.

C. Study Selection

Both authors, i.e., AFN and LDF, independently screened the titles and abstracts of all identified studies. Full texts of potentially eligible studies were then assessed for inclusion. Any disagreements were resolved through discussion.

D. Data Extraction

Data extraction was performed independently by the two authors using a standardized form. The following information was extracted: first author, year of publication, study design, sample size, patient demographics, clinical characteristics, tumor features, etiology, liver function, or disease stage. Discrepancies in data extraction were resolved through consensus.

E. Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). Two authors independently performed the quality assessment, with disagreements resolved through discussion.

F. Data Synthesis

Due to the anticipated heterogeneity in study designs and reported outcomes, a narrative synthesis approach was adopted. Results were summarized descriptively, with quantitative data presented as ranges or weighted means where appropriate. Subgroup analyses were performed based on geographical regions within Indonesia when sufficient data were available.

III. RESULTS

This systematic review analyzed data from 10 studies conducted across various regions in Indonesia, encompassing a total of 1,389 patients diagnosed with hepatocellular carcinoma (HCC). The studies were conducted in major cities including Jakarta, Mataram, Medan, Yogyakarta, and Samarinda, providing a diverse geographical representation of HCC characteristics in Indonesia. **Figure 1** showed the overall PRISMA flow diagram of this study, while **Table 1** summarized the included studies.

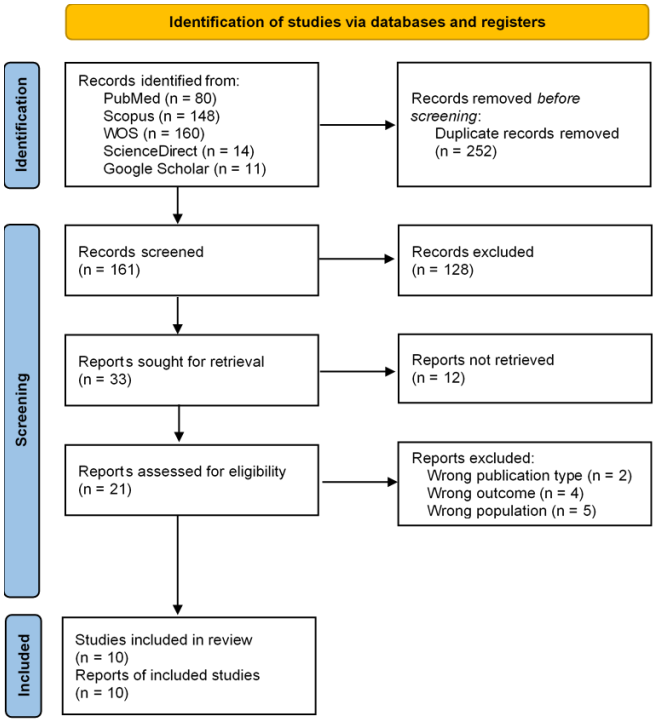

Figure 1. PRISMA flow diagram of the study.

Disease Stage at Presentation

Five studies, comprising 738 patients, reported on the Barcelona Clinic Liver Cancer (BCLC) staging system. The analysis revealed a predominance of intermediate to advanced stages (B and C) at diagnosis. Specifically, BCLC stage B ranged from 22.3% to 46.2%, while stage C ranged from 18.4% to 60.87% across studies. Notably, the proportion of patients presenting with early-stage disease (BCLC A) was consistently low, ranging from 1.8% to 19.2%, with one study reporting 53.8%. Late-stage presentation (BCLC D) varied widely, from 5.4% to 39.13% across studies.

Liver Function

Data on Child-Pugh scores were available from 7 studies, encompassing 843 patients. The distribution of liver function varied considerably across studies. Child-Pugh A (well-compensated liver disease) ranged from 12.0% to 85.7%, Child-Pugh B from 14.3% to 56.0%, and Child-Pugh C (advanced liver dysfunction) from 8.2% to 32.0%. This heterogeneity suggests significant variability in the severity of underlying liver disease among HCC patients in different regions of Indonesia.

Etiology

Hepatitis B virus (HBV) infection emerged as the primary etiological factor for HCC in Indonesia, with prevalence ranging from 53.8% to 84.0% across studies. Hepatitis C virus (HCV) infection was less common, with prevalence varying from 1.0% to 25.21%. Notably, non-viral etiologies represented a substantial proportion in some studies, reaching up to 37.4% of cases. The percentage of non-B non-C or non-viral HCC ranged from 2.9% to 39.0%, indicating a significant burden of HCC cases potentially related to metabolic factors or other etiologies.

Demographic and Clinical Characteristics

The mean age at diagnosis, reported in 6 studies, ranged from 52.43 to 63.1 years, suggesting that HCC in Indonesia primarily affects middle-aged to older adults. Gender distribution was not consistently reported across all studies.

Cirrhosis was a common comorbidity, with prevalence ranging from 45.1% to 78.1% in the three studies that reported this information. Metastatic disease was reported in only one study, with a prevalence of 12.5%.

Tumor characteristics, such as differentiation grading, were reported inconsistently across studies. In the two studies that provided this information, there was a wide range of differentiation patterns, from well-differentiated to poorly differentiated tumors.

Table 1. Summary of the included studies.

No	Author, Year	Place	N total of subjects	BCLC staging (n, %)	Hep B (+) (n, %)	Hep C (+) (n, %)	Non-B Non-C or Non-viral (+) (n, %)	Age at dx (Mean ± SD, years)	Child-Pugh (n, %)	Meta-stasis (n, %)	Cirrhosis (n, %)	Tumor differentiation grading
1	(Aprilicia et al., 2021)	Jakarta (RSCM)	295	A = 47 (15.9) B = 127 (43.1) C = 105 (35.6) D = 16 (5.4)	187 (63.4)	64 (21.7)	44 (14.9)	56 ± 12.18	A = 173 (58.6) B = 98 (33.2) C = 24 (8.2)	37 (12.5)	N/A	N/A
2	(Jasirwan et al., 2020)	Jakarta (RSCM, Dharmais Hospital)	282	A = 24 (8.5) B = 101 (35.8) C = 117 (41.5) D = 40 (14.2)	178 (63.1)	48 (17.0)	46 (16.3)	N/A	A = 137 (48.6) B = 107 (37.9) C = 38 (13.5)	N/A	164 (58.2)	N/A
3	(Syaiful et al., 2024)	Jakarta	91	A = 49 (53.8) B = 42 (46.2) C = - D = -	49 (53.8)	8 (8.8)	34 (37.4)	54 ± 21	A = 78 (85.7) B = 13 (14.3)	-	41(45.1)	Well = 8 (8.8) Moderate = 39 (42.9) Moderate to

									C = -			poor = 18 (19.8) Poor = 26 (28.6)
4	(Wang et al., 2002)	Mataram	101	N/A	10 (10.0)	1 (1.0)	39 (39.0)	63.1 ± 11.2	N/A	-	34 (47.0)	N/A
5	(Siregar & Buulolo, 2018)	Medan	100	N/A	84 (84.0)	5 (5.0)	11 (11.0)	57.2 ± 14.74	A = 12 (12.0) B = 56 (56.0) C = 32 (32.0)	N/A	N/A	N/A
6	(Suriapranata IM, 2010)	Jakarta	119	N/A	73 (61.34)	30 (25.21)	16 (13.45)	54.4 ± 13.1	N/A	N/A	N/A	N/A
7	(Effendi K, 2024)	Jakarta	35	N/A	28 (80.0)	6 (17.1)	1 (2.9)	N/A	N/A	N/A	N/A	Early—well diff = 3 Moderate = 18 Poor = 14
8	(Hasan et al., 2020)	Jakarta	114	A = 2 (1.8) B = 48 (42.1) C = 32 (28.1) D = 32 (28.1)	77 (67.5)	16 (14.0)	20 (17.5)	N/A	A = 53 (46.5) B = 31 (27.2) C = 30 (26.3)	N/A	89 (78.1)	N/A
9	(Ratnasari et al., 2016)	Yogyakarta	46	A = - B = - C = 28 (60.87) D = 18 (39.13)	26 (56.52)	5 (10.87)	15 (32.61)	52.43±12.78	A = 17 (36.96) B = 22 (47.83) C = 7 (15.22)	N/A	N/A	N/A
10	(Puri et al., 2021)	Samarinda	206	A = 19 (19.2) B = 46 (22.3) C = 38 (18.4) D = 43 (20.9)	129 (62.6)	8 (3.9)	69 (33.5)	54.3 (17—85)	A = 12 (12.6) B = 90 (43.7) C = 37 (18.0)	N/A	N/A	N/A

IV. DISCUSSION

This systematic review provides a comprehensive overview of hepatocellular carcinoma (HCC) characteristics in Indonesia, highlighting several key findings that have important implications for clinical practice and public health strategies. One of the most striking findings is the predominance of intermediate to advanced stage HCC at diagnosis, with BCLC stages B and C accounting for a significant proportion of cases across studies. This late-stage presentation is consistent with findings from other developing countries. For instance, Nandennavar et al. (2017) in India reported that 68% of HCC patients presented at BCLC stages C, while a multi-center study in Turkey by Akarca et al. (2021) found that 57% of patients were diagnosed at BCLC B-D stages (Akarca et al., 2021; Nandennavar et al., 2017). The high proportion of late-stage diagnoses in Indonesia emphasize the urgent need for improved screening and early detection programs, particularly for high-risk populations.

Hepatitis B virus (HBV) infection emerged as the primary etiological factor for HCC in Indonesia, with prevalence ranging from 53.8% to 84.0% across studies. This finding aligns with the broader Asian context, as demonstrated by a review by Kim (2024), which reported HBV as the predominant cause of HCC in most Asian countries (Kim, 2024). The high prevalence of HBV-related HCC in Indonesia emphasizes the critical importance of hepatitis B vaccination programs and antiviral therapy in HCC prevention strategies. Hepatitis C virus (HCV) infection was less common in our review, with prevalence varying from 1.0% to 25.21%. This lower prevalence of HCV-related HCC in Indonesia contrasts with some Western countries and Japan, where HCV is often the leading cause of HCC (Yang et al., 2019). However, the variability in HCV prevalence across studies suggests potential regional differences within Indonesia that warrant further investigation.

Notably, the substantial proportion of non-viral HCC cases (up to 37.4% in some studies) is a finding of particular interest. This trend is consistent with global observations of an increasing burden of non-alcoholic fatty liver disease (NAFLD)-related HCC (Kim, 2024). The high prevalence of non-viral HCC in Indonesia highlights the need for a broader approach to HCC prevention that addresses metabolic risk factors in addition to viral hepatitis.

The heterogeneity in Child-Pugh scores across studies reflects the complex interplay between HCC and underlying liver disease in the Indonesian population. The prevalence of cirrhosis among HCC patients (45.1% to 78.1%) is comparable to global estimates, which suggest that 80-90%

of HCC cases occur in the context of cirrhosis (Asafo-Agyei & Samant, 2024). However, the significant proportion of non-cirrhotic HCC cases in some studies would emphasize the importance of surveillance strategies that extend beyond cirrhotic patients in the Indonesian context.

The mean age at diagnosis ranging from 52.43 to 63.1 years is generally consistent with global trends, although slightly younger than what is typically observed in Western populations. For comparison, a large-scale study in the United States by Yang et al. (2017) reported a median age of 62 years at HCC diagnosis (Yang et al., 2017). The relatively younger age at diagnosis in Indonesia may reflect differences in risk factor exposure, genetic predisposition, or earlier onset of viral hepatitis infections.

Implications of Findings

The findings of this review have several important implications for HCC management in Indonesia. The high proportion of late-stage diagnoses calls for improved screening programs, particularly targeting high-risk groups such as chronic hepatitis B carriers and patients with cirrhosis. Moreover, the predominance of HBV-related HCC underscores the critical importance of hepatitis B vaccination and antiviral therapy as key preventive strategies.

Limitations

The heterogeneity in HCC characteristics across studies suggests potential regional differences within Indonesia, highlighting the need for tailored approaches to HCC prevention and management in different parts of the country. Future studies should focus on elucidating the factors contributing to late-stage presentation, investigating the rising trend of non-viral HCC, and evaluating the effectiveness of different screening and prevention strategies in the Indonesian context.

CONCLUSIONS

This systematic review provides valuable insights into the characteristics of HCC in Indonesia, revealing a complex landscape characterized by late-stage presentation, a high prevalence of HBV-related cases, and significant regional variability. These findings serve as a crucial foundation for developing targeted strategies to address the substantial burden of HCC in Indonesia and improve outcomes for patients affected by this devastating disease.

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