Clinicopathological Characteristics of Hepatocellular Carcinoma at a Tertiary Hospital: A Retrospective Study

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ABSTRACT

Background: *Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and shows significant regional variations in clinicopathological characteristics. Limited data exist on HCC patterns in Indonesia, particularly in West Sumatra. This study aimed to characterize the clinicopathological features of HCC at Dr. M. Djamil Hospital, Padang, from 2021to2024*

Methods: *A descriptive retrospective study was conducted using medical records and histopathological re-evaluation of 46 HCC cases. Specimens were examined for demographic data, tumor characteristics, histopathological subtypes according to the WHO 2019 classification, differentiation grade, lymphovascular invasion, and background liver pathology.*

Results: *The median age was 56 years, with male predominance (60.9%). Most specimens were resection specimens (60.9%) with tumor size ≥4 cm in 47.8% of cases and single nodules in 52.1%. Clear cell (39.1%) and macrotrabecular massive (37.0%) were the predominant subtypes, contrasting with global data showing NOS predominance. Most tumors were moderately differentiated (63.0%), with lymphovascular invasion present in 65.2% and cirrhotic background in 58.7% of cases*

Conclusion: *HCC in West Sumatra demonstrates distinct histopathological patterns, with a predominance of clear cell and macrotrabecular massive subtypes and high rates of lymphovascular invasion. These finding suggest histopathological features associated with aggressive tumor behavior (particularly macrotrabecular massive subtype and lymphovascular invasion), although no clinical outcome or survival analysis was performed.*

Keywords: *Hepatocellular Carcinoma, Histopathology, Lymphovascular Invasion*

ABSTRAK

Latar Belakang: *Karsinoma hepatoselular (KHS) merupakan kanker keenam tersering di dunia dengan variasi karakteristik klinikopatologis yang signifikan antar wilayah. Data mengenai pola KHS di Indonesia, khususnya Sumatera Barat, masih terbatas. Penelitian ini bertujuan melaporkan gambaran karakteristik klinikopatologis KHS di RSUP Dr. M. Djamil Padang tahun 2021-2024*

Metode: *Studi deskriptif retrospektif dilakukan menggunakan rekam medis dan reevaluasi histopatologi 46 kasus KHS. Spesimen diperiksa untuk data demografi, karakteristik tumor, subtipe histopatologi menurut klasifikasi WHO 2019, derajat diferensiasi, dan invasi limfovaskular.*

Hasil: *Median usia pasien adalah 56 tahun dengan dominasi laki-laki (60,9%). Sebagian besar jaringan diperoleh dari tindakan reseksi (60,9%). Ukuran tumor ≥4 cm ditemukan pada 47,8% kasus dan 52,1% berupa nodul tunggal. Subtipe clear cell (39,1%) dan macrotrabecular massive (37,0%) mendominasi, berbeda dengan data global yang umumnya didominasi subtipe NOS. Sebagian besar tumor menunjukkan diferensiasi sedang (63,0%). Invasi limfovaskular ditemukan pada 65,2% kasus dan 58,7% kasus terjadi pada hati yang sudah sirosis.*

Kesimpulan: *KHS di Sumatera Barat memiliki pola histopatologi yang khas dengan dominasi subtipe clear cell dan macrotrabecular massive disertai tingginya angka invasi limfovaskular. Temuan ini menunjukkan ciri-ciri histopatologis yang terkait dengan perilaku tumor yang agresif (terutama subtipe makrotrabekular masif dan invasi limfovaskular), meskipun tidak dilakukan analisis hasil klinis atau analisis kelangsungan hidup.*

Kata kunci: *Karsinoma Hepatoselular, Histopatologi, Invasi Limfovaskular*

INTRODUCTION

Hepatocellular carcinoma (HCC) represents a major global health challenge, ranking as the sixth most common cancer worldwide and the third leading cause of cancer-related mortality.[1] This primary liver malignancy accounts for approximately 80% of all primary liver cancers, with an estimated 866,136 new cases and 758,725 deaths reported globally in 2022.[2] The incidence of HCC varies significantly across different geographic regions, with the highest rates observed in East Asia (14.8 cases per 100,000 population annually) and Southeast Asia (9 cases per 100,000 population annually).[3] In Indonesia, the burden of HCC continues to rise, with the number of new cases projected to increase from 21,392 in 2020 to 39,273 by 2040,[4] highlighting the urgent need for comprehensive regional epidemiological data to guide healthcare planning and resource allocation.

The development of HCC is influenced by multiple risk factors, including advanced age, male sex, chronic hepatitis B and C infections, alcohol consumption, and non-alcoholic fatty liver disease (NAFLD).[5–7] The histopathological characterization of HCC has evolved significantly with the WHO classification of digestive system tumours 5th edition (2019), which categorizes HCC into nine distinct subtypes: fibrolamellar, scirrhous, clear cell, steatohepatitic, macrotrabecular massive, chromophobe, lymphocyte-rich, neutrophilic-rich, and NOS (not otherwise specified).[8] Each subtype exhibits unique histopathological features, molecular profiles, and prognostic implications that directly influence clinical management decisions.[8,9] Additionally, critical pathological parameters such as tumor differentiation grade, lymphovascular invasion, and background liver pathology serve as important prognostic indicators that guide therapeutic strategies and predict patient outcomes.[10,11]

Despite the global understanding of HCC epidemiology and pathology, significant knowledge gaps remain regarding the clinicopathological characteristics of HCC in specific regional contexts, particularly in Indonesia. Previous studies have demonstrated considerable geographic variations in HCC presentation, including differences in age distribution, etiological factors, and histopathological patterns between Asian and Western populations.[12] The heterogeneity of HCC characteristics across different populations underscores the importance of regional studies to understand local disease patterns. Currently, comprehensive data on HCC characteristics at tertiary referral centers in West Sumatra, Indonesia, remain limited, which hampers the development of tailored diagnostic and therapeutic approaches for the local population.

This study aims to address this critical knowledge gap by comprehensively analyzing the clinicopathological characteristics of HCC at Dr. M. Djamil Hospital, Padang, from 2021 to 2024. By examining demographic patterns, macroscopic tumor features, histopathological subtypes according to the WHO 2019 classification, tumor differentiation grades, lymphovascular invasion, and background liver pathology, this study provides essential epidemiological data for the West Sumatra region. The findings will serve as a foundation for future research, contribute to the understanding of regional HCC patterns, and potentially inform the development of more effective prognostic assessment and management strategies tailored to the local population.

METHODS

This was a retrospective study using secondary data obtained from medical records of patients diagnosed with hepatocellular carcinoma at the Pathology Laboratory of Dr. M. Djamil Hospital, Padang, during the period from January 2021 to July 2024. The study population comprised all HCC cases diagnosed at the laboratory during this period, with a total sampling method employed to include all cases that met the inclusion criteria. This study employed a total sampling approach, including all 46 eligible cases. Total sampling was selected to ensure comprehensive coverage of the available hepatocellular carcinoma (HCC) population, allowing the study to capture the full spectrum of characteristics and provide a complete overview of HCC cases during the study period. Inclusion criteria were patients with a confirmed

diagnosis of HCC who had complete medical record data including age, sex, sampling method (biopsy or resection), tumor size, number of nodules, and histopathological features. The exclusion criteria were cases in which Hematoxylin–Eosin (H&E)-stained slides or formalin-fixed paraffin-embedded (FFPE) tissue blocks could not be re-evaluated. Data were collected from pathology reports and patient medical records, and were supplemented by re-evaluation of H&E stained slides using an Olympus CX23 LED binocular microscope at magnifications of 40x, 100x, and 400x.

The histopathological re-evaluation assessed HCC subtypes according to the WHO classification of digestive system tumours 5th edition (2019), which categorizes HCC into nine subtypes: fibrolamellar, scirrhous, clear cell, steatohepatitic, macrotrabecular massive, chromophobe, lymphocyte-rich, neutrophilic-rich, and NOS (not otherwise specified) . Additionally, tumor differentiation was graded using the three-tiered WHO grading system (well-differentiated/grade 1, moderately-differentiated/grade 2, and poorly-differentiated/grade 3), and the presence of lymphovascular invasion and background liver pathology (cirrhotic versus non-cirrhotic) was evaluated. Lymphovascular invasion (LVI) was defined as the presence of tumor cell clusters within endothelial-lined vascular or lymphatic spaces identified on Hematoxylin-Eosin (H&E) stained sections. Microvascular invasion referred to tumor emboli within small vascular channels (including small portal venules or hepatic venules), whereas macrovascular invasion referred to involvement of larger identifiable vessels. LVI assessment was performed on both resection and biopsy specimens whenever available. In biopsy specimens, LVI was recorded only when unequivocally identifiable within the sampled tissue, acknowledging the limitations of sampling volume. Statistical analysis was performed using descriptive statistics, with data presented as frequencies and percentages in distribution tables. The study received ethical approval from the Ethics Committee of Dr. M. Djamil Hospital, Padang (No. DP. 04.03/D.XVI/427/2024).

RESULTS

A total of 46 patients with hepatocellular carcinoma were identified during the study period. The demographic and clinical characteristics are summarized in **Table 1.** The median age at diagnosis was 56 years (range: 32-87 years), with 32 patients (69.6%) aged ≥50 years and 14 patients (30.4%) aged <50 years. Male predominance was observed. with 28 cases (60.9%) compared with 18 female cases (39.1%), yielding a male-to-female ratio of 1.6:1. Regarding specimen type, resection specimens comprised the majority (28 cases, 60.9%), followed by biopsy specimens (17 cases, 37%), with one case (2.2%) having an unknown sampling method.

Table 1. Demographic and Clinical Characteristics of Hepatocellular Carcinoma Patients (N=46)

Characteristics	n	%
Age (years)		
<50	14	30.4
≥50	32	69.6
Sex		
Male	28	60.9
Female	18	39.1
Sampling method		
Biopsy	17	37.0
Resection	28	60.9
Unknown	1	2.2
Tumor size		
<2 cm	12	26.1
2-<4 cm	10	21.7
≥4 cm	22	47.8
Unknown	2	4.3
Number of nodules		
Single	24	52.1
Multiple	12	26.0
Unknown	10	21.7

Macroscopic examination revealed that tumor size was ≥4 cm in 22 cases (47.8%), <2 cm in 12 cases (26.1%), and 2-<4 cm in 10 cases (21.7%), with size data unavailable in 2 cases (4.3%). Single nodules were identified in 24 cases (52.1%) and multiple nodules in 12 cases (26.0%), while the number of nodules could not be determined in 10 cases (21.7%). It should be noted that a relatively high proportion of cases had missing data regarding the number of nodules (21.7%) and tumor size (4.3%), reflecting limitations inherent in retrospective record-based studies.

Histopathological re-evaluation according to the WHO 2019 classification revealed diverse HCC subtypes **(Table 2 and Figure 1).** The clear cell subtype was the most frequent (18 cases, 39.1%), followed by macrotrabecular massive subtype (17 cases, 37.0%). Other subtypes included scirrhous (4 cases, 8.7%), NOS (3 cases, 6.5%), steatohepatitic (2 cases, 4.3%), and one case each (2.2%) of lymphocyte-rich and neutrophilic-rich subtypes. Notably, no cases of the fibrolamellar or chromophobe subtypes were identified.

Table 2. Histopathological Characteristics of Hepatocellular Carcinoma (n=46)

Characteristics	n	%
Histopathological subtype		
Clear cell	18	39.1
Macrotrabecular massive	17	37.0
Scirrhous	4	8.7
NOS	3	6.5
Steatohepatitic	2	4.3
Lymphocyte-rich	1	2.2
Neutrophilic-rich	1	2.2
Fibrolamellar	0	0
Chromophobe	0	0
Differentiation grade		
Grade 1 (well-differentiated)	5	10.9
Grade 2 (moderately-differentiated)	29	63.0
Grade 3 (poorly-differentiated)	12	26.1
Lymphovascular invasion		
Present	30	65.2
Absent	16	34.8
Background liver pathology		
Cirrhotic	27	58.7
Non-cirrhotic	19	41.3

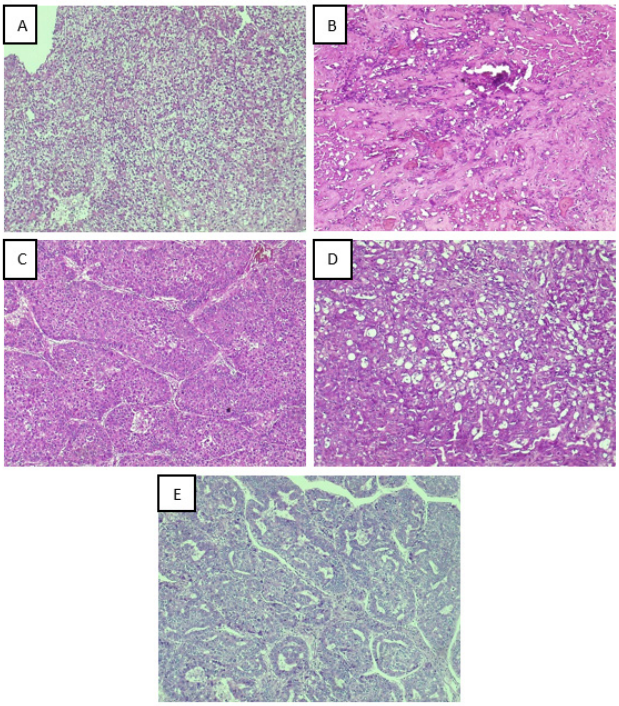

Figure 1. Representative histopathological subtypes of hepatocellular carcinoma. (A). Clear cell subtype showing tumor cells with clear cytoplasm due to glycogen accumulation, (B). Scirrhous subtype demonstrating dense intratumoral fibrosis, (C). Macrotrabecular massive subtype with trabeculae composed of more than 10 cells, (D). Steatohepatitic subtype exhibiting features of steatohepatitis including fat vacuoles and Mallory-Denk bodies ; (E) NOS subtype with pseudogland features. (H&E, 100x)

Tumor differentiation assessment showed that the majority of cases were moderately-differentiated (grade 2; 29 cases, 63.0%), followed by poorly-differentiated (grade 3; 12 cases, 26.1%) and well-differentiated tumors (grade 1; 5 cases, 10.9%). The histological grading patterns are illustrated in **Figure 2,** demonstrating the progressive loss of hepatocellular architecture and increasing degrees of nuclear atypia with higher tumor grades.

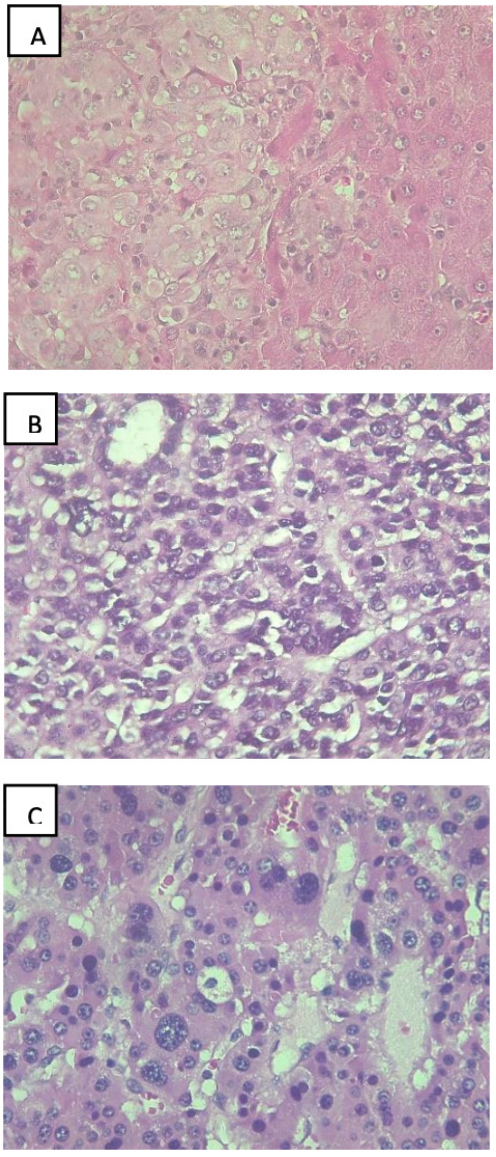

Figure 2. Histological differentiation grades of hepatocellular carcinoma. (A). Well-differentiated (Grade 1) showing thin trabecular pattern with minimal nuclear atypia (B). Moderately-differentiated (Grade 2) displaying trabecular thickness of at least 3 cells with moderate nuclear atypia, (C). Poorly-differentiated (Grade 3) exhibiting marked pleomorphism with prominent nucleoli and giant cells. (H&E, 400x)

Lymphovascular invasion was identified in 30 cases (65.2%), while 16 cases (34.8%) showed no evidence of lymphovascular invasion **(Figure 3).** Evaluation of background liver pathology revealed cirrhosis in 27 cases (58.7%) and non-cirrhotic liver parenchyma in 19 cases (41.3%), with the latter predominantly showing features of steatohepatitis **(Figure 4).**

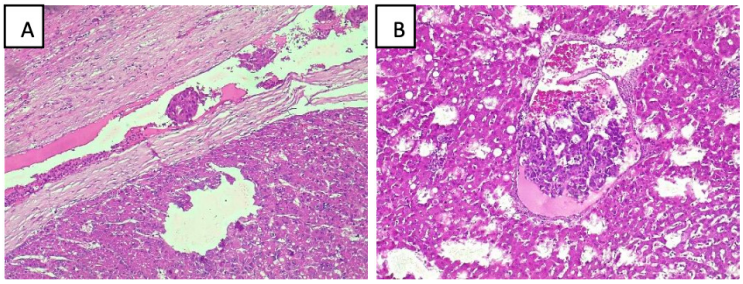

Figure 3. Pathological features of hepatocellular carcinoma. (A-B) Lymphovascular invasion showing tumor cell emboli within vascular spaces. (H&E, 100x)

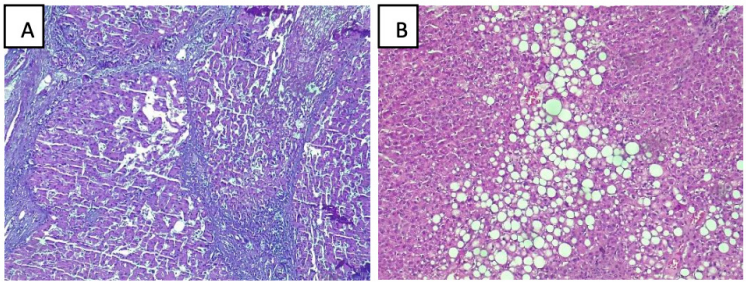

Figure 4. Illustration of non-tumorous liver lesions. (A). Cirrhotic, (B). Non-cirrhotic including steatohepatitis or fatty liver (100x)

DISCUSSION

This study provides comprehensive clinicopathological data on hepatocellular carcinoma from a tertiary referral center in West Sumatra, Indonesia, revealing several important findings that contribute to the regional understanding of HCC. The predominance of patients aged ≥50 years (69.6%) in our cohort aligns with global epidemiological trends, consistent with findings by Iuliana et al., who reported that the majority of their 1,547 HCC patients were older than 60 years..[13] Similarly, research from Indonesia by Irsan et al. found a mean age of 55 years among HCC patients,[14] supporting the observation that HCC primarily affects older adults in Southeast Asian populations. The male predominance observed in our study (60.9%) with a male-to-female ratio of 1.6:1, while notable, was less pronounced than reported in other studies, such as Iuliana et al., who found that 84.1% of patients were male patients,[13] suggesting potential regional variations in sex distribution that may reflect differences in risk factor exposure or genetic susceptibility.

A striking finding in our study was the distribution of histopathological subtypes, with clear cell (39.1%) and macrotrabecular massive (37.0%) subtypes comprising the majority of cases, contrasting markedly with WHO data indicating that approximately 65% of HCC cases are typically classified as NOS.[15] This discrepancy may reflect regional genetic variations, environmental factors unique to our population, or differences in histopathological interpretation practices. The high prevalence of the macrotrabecular massive subtype is particularly concerning, as this variant is associated with poor prognosis, higher serum AFP levels, and an increased likelihood of vascular invasion.[11] Ziol et al. reported macrotrabecular massive subtype in only 12% of their cohort,[16] suggesting our population may have distinct tumor biology requiring tailored therapeutic approaches. The predominance of these specific subtypes warrants further molecular investigation to better understand the underlying pathogenic mechanisms and potential therapeutic targets. Several factors may explain the unusually high prevalence of clear cell and macrotrabecular massive subtypes in our cohort. First, as a tertiary pathology referral center, our institution may receive cases with more advanced or morphologically distinctive tumors (referral bias). Second, this study included only histologically confirmed HCC cases, excluding radiologically diagnosed cases, which may have influenced subtype distribution (case selection bias). Third, immunohistochemical and molecular analyses were not routinely performed; therefore, subtype classification relied exclusively on morphological criteria, which may contribute to classification variability.

The high prevalence of lymphovascular invasion (65.2%) in our cohort represents a critical prognostic finding with significant clinical implications. This rate exceeds that reported by Yamashita et al., who

found vascular invasion in 28.9% of small HCCs.[17] The presence of lymphovascular invasion is a well-established predictor of poor outcomes, with systematic reviews demonstrating its adverse impact on both disease-free survival and overall survival.[18] Our findings suggest that patients in our region may present with more aggressive disease or at more advanced stages, emphasizing the need for enhanced surveillance programs and earlier detection strategies. The combination of high-grade tumors (26.1% poorly-differentiated) and frequent vascular invasion indicates an aggressive disease phenotype that may require more intensive therapeutic interventions.

The unexpectedly high rate of lymphovascular invasion (65.2%), despite the predominance of resection specimens, may reflect several factors. As a tertiary referral center, Dr. M. Djamil Hospital may receive more advanced or complex cases, potentially introducing referral bias. Additionally, histopathological evaluation of resection specimens allows more extensive tissue sampling, which may increase the detection rate of vascular invasion compared with biopsy-only cohorts. Nevertheless, the possibility of overestimation due to sampling concentration on tumoral areas cannot be entirely excluded. The inference of aggressive tumor behavior in our study is based solely on histopathological parameters (macrotrabecular massive subtype and lymphovascular invasion) and not on clinical outcomes or survival data, as follow-up information was not available .

The observation that 58.7% of cases occurred in cirrhotic livers aligns with the established understanding of HCC pathogenesis, as cirrhosis remains the strongest risk factor for HCC development.[5,6] However, the substantial proportion of non-cirrhotic cases (41.3%) merits attention, as these patients may have distinct etiological factors and potentially better surgical outcomes. Kumar et al. reported cirrhosis in 72.5% of HCC patients,[5] suggesting that our population may have a higher proportion of non-cirrhotic HCC, possibly related to the increasing prevalence of NAFLD-associated HCC in the region. The predominance of steatohepatitis features in non-cirrhotic livers supports this hypothesis and reflects global trends in metabolic syndrome-associated HCC.[7]

Our study revealed that most specimens were obtained through resection (60.9%) rather than biopsy, indicating that a significant proportion of patients were surgical candidates at the time of presentation. This finding is encouraging, as it suggests that potentially curative treatment options were available for the majority of patients. The tumor size distribution, with 47.8% of tumors ≥4 cm, combined with the 52.1% rate of single nodules, provides insight into the stage of disease at presentation. While larger tumors generally confer a worse prognosis, the predominance of single nodules suggests that many patients may still benefit from surgical intervention.[11,19]

The clinical implications of our findings are multifaceted. The high prevalence of aggressive histological subtypes and lymphovascular invasion suggests that adjuvant therapy should be strongly considered even after curative resection. The identification of specific HCC subtypes may guide personalized treatment approaches, as different subtypes respond variably to systemic therapies.[20,21] Furthermore, the significant proportion of non-cirrhotic HCC cases highlights the need for expanded screening criteria beyond traditional high-risk groups with cirrhosis.

This study has several limitations that should be acknowledged. The retrospective design and reliance on medical records may have introduced selection bias and limited the availability of certain clinical parameters. The relatively small sample size of 46 cases, while providing valuable regional data, may not fully represent the broader HCC population in Indonesia. Additionally, the absence of molecular characterization and long-term follow-up data limits our ability to correlate histopathological findings with clinical outcomes and treatment responses.

This study has several limitations. First, its retrospective descriptive design precluded inferential statistical analyses and the assessment of associations between variables. Second, incomplete medical records resulted in missing data for certain clinicopathological parameters. Third, etiological factors such as hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol consumption, and non-alcoholic fatty liver disease (NAFLD) were not consistently available and therefore could not be systematically analyzed. Consequently, histopathological findings could not be correlated with the underlying liver disease etiology or serum biomarkers such as alpha-fetoprotein (AFP) and PIVKA-II. Additionally, immunohistochemical and molecular analyses were not routinely performed, and long-term follow-up data were unavailable, preventing the correlation between histopathological features and survival outcomes.

Future research should focus on prospective studies with larger cohorts to validate these findings

and establish region-specific prognostic models. Molecular profiling of the predominant clear cell and macrotrabecular massive subtypes in our population could reveal targetable mutations and guide precision medicine approaches. Long-term outcome studies correlating histopathological features with survival data would provide valuable prognostic information for clinical decision-making. Additionally, investigations into the etiological factors contributing to the high prevalence of specific HCC subtypes in our region could inform prevention strategies.

CONCLUSION

This study provides essential clinicopathological characterization of hepatocellular carcinoma in West Sumatra, Indonesia, revealing a predominance of clear cell and macrotrabecular massive subtypes, high rates of lymphovascular invasion (65.2%), and moderate differentiation in the majority of cases. (63.0%). The findings demonstrate distinct regional patterns that differ from global data, particularly the unexpected distribution of histopathological subtypes and the aggressive disease phenotype characterized by frequent vascular invasion. These results have important implications for clinical management, suggesting the need for aggressive adjuvant therapy protocols, enhanced surveillance strategies for early detection, and consideration of region-specific prognostic models. The data establish a foundation for future prospective studies and molecular investigations that could guide the development of tailored therapeutic approaches for HCC patients in Indonesia and similar Southeast Asian populations. The aggressive phenotype described in this study refers to histopathological indicators rather than documented clinical outcomes.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related with this study.

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AUTHOR CONTRIBUTIONS

RAR prepared the background section, compiled the relevant literature forming the basis of the study, managed the ethical clearance process, and conducted data collection and processing. NH performed data synthesis, study validation, and data analysis. AA, Y, and LD contributed to manuscript revision and provided critical feedback.

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DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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