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The relationship between thrombus occurrence based on nodule type in hepatocellular carcinoma patients undergoing abdominal CT scan examination at Dr. Soetomo regional general hospital, Surabaya

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Abstract

Hepatocellular Carcinoma (HCC) is the most common primary liver malignancy and generally develops against a background of chronic liver disease. One important complication of HCC is the formation of tumor thrombus in the portal vein, which is closely associated with poor prognosis. This study aims to analyze the relationship between hepatocellular carcinoma nodule types and the occurrence of portal vein thrombus based on contrast-enhanced abdominal CT scan findings. This study is an observational analytical study with a cross-sectional design using retrospective data from HCC patients who underwent multiphase abdominal CT scan examination at the Radiology Installation of Dr. Soetomo Regional General Hospital from January 2024 to June 2025. HCC nodules were classified into four types: encapsulated nodular, simple nodular with extranodular growth, multinodular confluent, and infiltrative type. Thrombus occurrence was categorized as no thrombus, thrombus in portal vein branches, and thrombus in the main portal vein. Relationship analysis was performed using Spearman correlation test. A total of 59 research subjects met the inclusion criteria. The most common nodule type found was infiltrative type (49.2%), followed by multinodular confluent type (39.0%). Portal vein thrombus occurrence was found in 52.5% of cases, with the most involvement in the main portal vein. Analysis results showed a statistically significant relationship between HCC nodule type and portal vein thrombus occurrence ($p = 0.000$; $r = 0.610$), with a strong positive correlation. Infiltrative nodule type had the highest tendency for thrombus formation, especially in the main portal vein. The conclusion of this study shows that hepatocellular carcinoma nodule type is significantly related to portal vein thrombus occurrence. This finding confirms the importance of evaluating nodule characteristics on CT scan as part of thrombus risk assessment and HCC patient management planning.

Keywords: Hepatocellular carcinoma, Liver nodules, Portal vein thrombus, Abdominal CT scan, Tumor thrombus

Introduction

Accounting for over 90% of primary liver cancer cases, Hepatocellular Carcinoma (HCC) is the most prevalent form of this malignancy.[1–3] Cirrhosis is a major risk factor for Hepatocellular Carcinoma (HCC), with about 85% of HCC patients having this underlying condition. Worldwide, HCC is now the fifth most frequently diagnosed cancer.[4,5] Hepatocellular Carcinoma (HCC) is an aggressive liver cancer. For men, it is the second most common cause of cancer death, trailing only lung cancer. The outlook is serious; only about 18% of patients survive five years, a rate worse than all cancers except pancreatic cancer. It most often develops in people with underlying liver damage. The key risk factors are long-term hepatitis B or C infections, heavy alcohol use, and fatty liver disease. Most patients (80-90%) who get HCC already have cirrhosis. For these patients, the yearly chance of developing HCC is 2-4%. A liver transplant is a potential cure, but only for patients whose tumors are small and few in number. If the cancer has spread into major blood vessels or outside the liver, a transplant is not an option.

Advanced Hepatocellular Carcinoma (HCC), one of the most common malignant tumors, is frequently characterized by the development of a tumor thrombus. This thrombus most often involves the portal or hepatic veins.[6,7] Tumor thrombus formation is a poor prognostic indicator in Hepatocellular Carcinoma (HCC), an aggressive malignancy known for invading blood vessels. This invasion commonly leads to thrombi in major vessels like the portal or hepatic veins. The thrombus is categorized by its anatomical location relative to the heart, a classification that directly guides the surgical strategy when operative treatment is considered.

Proving to be an independent marker of poor outcomes, Portal Vein Tumor Thrombus (PVTT)

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drastically shortens survival in HCC patients. Whether present at diagnosis or developing later due to recurrence, patients with PVTT have a median survival of only about three months under optimal supportive care.[8] The presence and extent of Portal Vein Tumor Thrombus (PVTT) are key determinants of HCC prognosis. This is supported by a study from Giannelli et al.[9] which analyzed 150 HCC cases and found PVTT to be the most reliable predictor of poor survival. Additionally, the analysis reported a significant correlation, suggesting that more aggressive, poorly differentiated tumors have a higher propensity for vascular invasion.

HCC invades major vessels through stromal and endothelial destruction, leading to complications like flow-limiting stenosis or thrombus formation.[10] Patients with Portal Vein Tumor Thrombosis (PVTT) have a life expectancy of just two to four months with supportive care alone. The disease advances as tumor cells multiply inside blood vessels, acting as a foundation for thrombus development. If these thrombi become coated with endothelium, they evade the clotting system and show a greater propensity to spread, especially to the lungs. These viable microthrombi can lodge in distant capillaries, establishing a pathway for metastasis.

Literature Review

Liver nodules

The liver is one of the organs where malignant, benign, primary, and secondary nodules can form. Liver nodules can also be solitary or multiple. The current widespread application of non-invasive imaging techniques facilitates liver evaluation[11], thereby increasingly improving the detection of small liver nodules with great clinical benefit, so that when liver nodules are found, further examination is needed to determine the presence of chronic liver disease associated with HCC.[12–14] In patients with chronic liver disease, conventional abdominal ultrasound serves as the initial, non-invasive, cost-effective, and widely accessible imaging tool to suggest a diagnosis of HCC.[15–17] The widespread adoption of initial ultrasound screening and subsequent CT and MRI has increased the identification of liver lesions, especially nodules.[18] Within a cirrhotic liver, all nodules should be presumed to be HCC until disproven. This high index of suspicion is crucial for early-stage diagnosis and enables potentially curative treatments like resection, ablation, or transplantation. Once a nodule is identified on ultrasound, the next diagnostic step is usually a dynamic contrast-enhanced CT or MRI for further characterization.[19,20] On enhanced contrast imaging, hepatocellular carcinoma (HCC) typically exhibits two classic diagnostic features: arterial hypervascularity and subsequent washout [21].

Hepatocellular carcinoma

Hepatocellular Carcinoma (HCC) constitutes 75–85% of primary liver cancers, followed by intrahepatic cholangiocarcinoma (10–15%). It holds significant global burden, ranking as the sixth most common cancer worldwide and the third leading cause of cancer death; its prognosis remains poor, with a five-year survival of merely 15%. In the United States, HCC incidence has tripled since 1980, designating it the fastest-rising tumor. Furthermore, mortality rates climbed by 43% between 2000 and 2016.

Hepatocellular Carcinoma (HCC) has an annual incidence of 1-6% in patients with cirrhosis. Primary risk factors include cirrhosis itself, alcohol use, hepatitis B and C infections, metabolic liver diseases, and certain hormonal therapies. Although HCC predominantly arises in cirrhotic livers, there is growing recognition of its occurrence in non-cirrhotic patients with non-alcoholic fatty liver disease. In a cirrhotic patient, clinical features such as new abdominal pain, rapid liver enlargement, weight loss, or the rare presentation of hemoperitoneum should prompt suspicion for HCC.[22–24] In cirrhotic patients progressing to HCC, common laboratory markers include a sharp rise in alkaline phosphatase, elevated AST/ALT, and erythrocytosis. Paraneoplastic manifestations such as hypoglycemia, hypercalcemia, hypercholesterolemia, or persistent leukocytosis may also occasionally be observed.

Tumor thrombus in HCC

Hepatocellular Carcinoma (HCC) invades major vessels by degrading the stromal and endothelial layers, potentially causing flow-impeding stenosis or thrombus formation. The latter, particularly in the form of Portal Vein Tumor Thrombosis (PVTT), carries a dire prognosis, with life expectancy limited to 2-4 months under best supportive care. The metastatic mechanism involves intravascular tumor cell proliferation. These cells can either act as a nidus for thrombus formation or become endothelial-lined, thereby evading the coagulation cascade. Such endothelialized microthrombi can remain viable within distant capillary beds, including the pulmonary and hepatic circulations, establishing a direct pathway for distant metastasis.

Tumor thrombus in hepatocellular carcinoma (HCC) is the invasion of tumor mass into the blood vessel lumen, most often involving the portal vein (PVTT, portal vein tumor thrombus), hepatic vein (HVTT), or in advanced cases can reach the inferior vena cava or even the right atrium. Detection and characterization of tumor thrombus is very critical in determining the stage, therapy, and prognosis of HCC. Tumor thrombus in HCC can be recognized through thrombus enhancement on contrast-based imaging (ultrasound, CT, MRI), vessel dilatation, contiguous relationship with primary tumor, FDG uptake on PET, and restricted diffusion on MRI[25–27]. The presence of tumor thrombus on imaging is strongly associated with decreased survival and affects exclusion from liver transplantation and aggressive surgery according to international criteria.

Conceptual framework

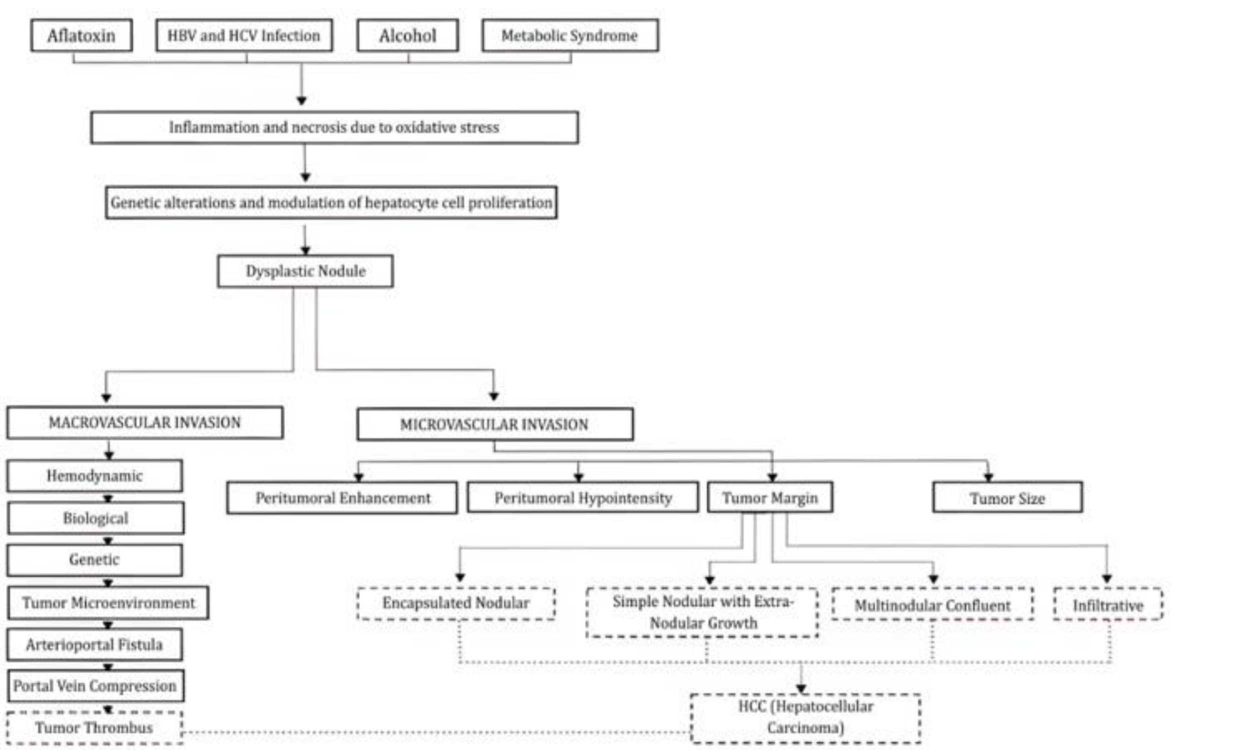

Fig 1. Conceptual framework

Research hypothesis

H0: There is no relationship between HCC nodule type and thrombus occurrence

H1: There is a relationship between HCC nodule type and thrombus occurrence

Variables·studied.·----------------¶
Variables·not·studied·________¶

Materials and Methods

Research design

This research is an observational analytical study with a cross-sectional design using retrospective data.

Research population and sample

1. Target Population: Data results of HCC

patients with contrast-enhanced abdominal CT scan

2. Accessible Population: Data of HCC patients with liver nodules who underwent abdominal CT scan examination at the Radiology Installation of RSUD Dr. Soetomo from January 2024 - June 2025
3. Research Sample: The research sample is the accessible population that meets the inclusion criteria.
4. Sample Size: The sample size in this study was calculated using the sample size formula for correlation tests as follows:

$$n = \frac{Z_{1-\alpha/2}^{2} P(1-P)}{d^{2}}$$

n = minimum sample size

d = error level = set at 0.15

Z 1/2α at 95% confidence level = standard value = 1.96

P = Proportion in population 0.5

Q = 1-p : 0,5

Based on the minimum sample size formula calculation, at least (42.8) 43 samples participating in this study are required to produce a research power of 95%.

Research criteria

1. Inclusion criteria

a) Patients meeting HCC diagnostic criteria, based on LIRADS criteria
b) Patients who underwent contrast-enhanced abdominal CT scan examination

Exclusion criteria

a) Incomplete three-phase CT scan images (arterial, venous, and delayed)
b) Patients with a history of secondary liver cancer
c) Patients who have undergone liver embolization therapy (TACE)

Research location and time

The research was conducted at the Radiology Installation of RSUD Dr. Soetomo Surabaya from January 2024 - June 2025.

Research variables

1. Liver nodule categories in HCC performed on MDCT Abdominal Scan, where nodules are classified into 4 types: encapsulated nodular, simple nodular with extranodular growth, multinodular confluent, and infiltrative
2. Formation of thrombus or not in the portal vein (portal vein branches or main portal)

Research instruments

CT Scan Equipment

CT Scan machine used at the Radiology Installation of Dr. Soetomo Regional General Hospital Surabaya.

Operational definitions

Table 1. Operational definitions

Variable	Definition	Methods	Scale
Liver Nodules	Primary lesions in the liver (not metastatic lesions) where in the arterial phase liver nodule enhancement is found followed by washout in the portal or delayed phase ("wash in and wash out"), grouped by type: Encapsulated nodular Simple nodular with extranodular growth Multinodular confluent Infiltrative type	Grouping CT scan results of HCC patients based on nodule type; CT scans re-read by radiology specialist operator with more than 10 years of experience.	Nominal

Thrombus	A condition where tumor cells invade and form blood clots inside large blood vessels/main blood vessels in the liver. This condition is a serious complication, especially in HCC cases and is associated with poor prognosis	Contrast-enhanced abdominal CT scan with images categorized based on the presence or absence of tumor thrombus, involvement of portal branches or main portal; CT scans re-read by radiology specialist operator with more than 10 years of experience.	Ordinal

Data collection and analysis

1. Data collection

Abdominal CT scan measurements and research data were collected by advanced-level radiology residents. This process was conducted under the direct supervision and guidance of two consultant abdominal radiologists, each with approximately ten years of specialized experience.

2. Data analysis

Data from CT scan examination results are collected and compiled into case report forms. After all data have been collected, the data are analyzed using the Statistical Programme for Social Sciences (SPSS) version 25.0.

a. Descriptive analysis

Each examination result obtained will be grouped by age, gender, and research variables which are then assessed for frequency and distribution.

b. Qualitative analysis

The bivariate test in this study aims to find the correlation between the potential for thrombus occurrence in the four HCC nodule types. The statistical analysis used is ordinal regression because the data analyzed in the dependent variable is ordinal scale and aims to find potential. P value is considered significant if $p<0.05$ with a 95% confidence interval. Statistical analysis results will be displayed in tables. From the ordinal regression results, coefficient values will be known that indicate the direction of relationship and strength of relationship as well as show which are significantly related in each category of tumor thrombus and its nodules.

Research ethics

The author submitted research approval to the Ethics Committee of the Faculty of Medicine, Airlangga University Surabaya/ Dr. Soetomo General Regional Hospital Surabaya.

Table 2. Descriptive demographic characteristics and normality test

Demographics	Descriptive (n=59)	p normality
Gender		
Male	45 (76,3%)	-
Female	14 (23,7%)	
Age		
Range (Median)	30 - 85 (55,0)	0,200
Mean ± Sd	56,17 ± 12,438	

*stated as normal data if p normality > 0.05

Results

Descriptive demographics of research

Based on research samples according to inclusion and exclusion criteria, 59 samples or subjects were obtained. Demographic descriptions include gender and age. The following table presents the results of demographic characteristics and data normality tests presented in the form of frequency and percentage for categorical data and range values, median, mean, and standard deviation for numerical data:

Based on the results of Table 1, descriptive demographics from 59 research subjects based on gender showed 45 male samples with a percentage of 76.3%, while females were 14 samples with a percentage of 23.7%, which means the gender description of subjects showed that most subjects were male. For descriptive demographic age from 59 samples, the age range was from 30 to 85 years with a median age of 55.0 years, for the mean and standard deviation of age was 56.17 ± 12.438, which means the age description of subjects showed that subject age based on mean falls into middle age/middle adulthood (40-59 years).

Based on the results of Table 1 for the normality test on demographic data using the Kolmogorov test because sample > 50, the p value for normality test for age data was 0.200, which is > 0.05, meaning that age data is stated to be normally distributed data.

Agreement test for nodule and thrombus assessment: Nodule and thrombus measurements in this study were assessed by 2 expert assessors/observers, where each assessor will assess nodules and thrombus in each subject. Because nodule and thrombus data are subjective assessment data from 2 assessors, an agreement test was conducted using the Kappa test to ensure that the subjectivity of the 2 assessors is stated to be the same. In the agreement test, the Kappa test is stated to have agreement or similarity in assessment if the p test value < 0.05 and the Kappa coefficient value falls into the strong category (0.600 - 0.800) or very strong (0.800 - 1.00). The following table shows the agreement test results for nodules and thrombus:

Table 3. Nodule and thrombus agreement test

Data Assessment	n	Agreed Data	Error Data	Kappa Coefficient	p value	Description
Nodul	59	55 (93,3%)	4 (6,7%)	0,888	0,000	Very strong
Trombus	59	59 (100%)	0 (0%)	1,000	0,000	Very strong

*stated as agreement/agreement occurs if p < 0.05

Table 3 shows the agreement test results for nodule and thrombus assessment. The number of data analyzed was 59 subjects. In nodule assessment, there were 55 data with a percentage of 93.3% that were consistent or agreed between assessor 1 and assessor 2, while inconsistent or error data were 4 cases with a percentage of 6.7%. The Kappa coefficient value obtained was 0.888 with a p value of 0.000, which is significant. This shows that the level of agreement in nodule assessment is in the very strong category. In thrombus assessment, all data, namely 59 cases, showed consistency or agreement with a percentage of 100%, so there was no error data between assessor 1 and assessor 2. The Kappa coefficient value obtained was 1.000 with a p value of 0.000, which is significant. Thus, the level of thrombus assessment agreement is also in the very strong category.

Based on the agreement test between assessor 1 and assessor 2, there was similarity in subjectivity in assessing nodules and thrombus, so the nodule and thrombus data in this study can be used, and in this study, for subsequent tests, both nodule and thrombus data use values from the 2 assessors combined into one, where those stated as not the same, the data taken/used is based on the highest degree/value.

Descriptive nodule and thrombus variables

Nodule variable measurement based on 4 categories/criteria, namely: Encapsulating, Simple nodular with extranodular growth, Multinodular confluent, and Infiltrative. While for the thrombus variable based on 4 categories/criteria, namely: None, Present only in portal branches, and Present in main portal. The following table shows the descriptive results of nodule and thrombus measurement variables where data is presented in the form of frequency and percentage:

Table 4. Descriptive nodules and thrombus

Variable	Descriptive (n=59)
Nodul	
Encapsulating	2 (3,4%)
Simple nodular with extranodular growth	5 (8,5%)
Multinodular confluent	23 (39,0%)
Infiltrative	29 (49,2%)
Thrombus	
None	28 (47,5%)
Present only in portal branches	9 (15,3%)
Present in main portal	22 (37,3%)

Table 4 presents the distribution of nodule types and thrombus presence in 59 research subjects. In the nodule variable, most cases were found with infiltrative type, namely 29 cases or 49.2%. Next, multinodular confluent type was found in 23 cases or

39.0%. Simple nodular with extranodular growth type was recorded in 5 cases or 8.5%, while encapsulating type was the least found, namely only 2 cases or 3.4%. Thus, the most dominant nodule pattern in this study was infiltrative type. In the thrombus variable, almost half of the subjects had no thrombus, namely 28 cases or 47.5%. Thrombus in portal branches was found in 9 cases or 15.3%, while thrombus in the main portal was found in 22 cases or 37.3%. This shows that although almost half of the subjects did not have thrombus, in cases with thrombus, most were found in the main portal.

Analysis of relationship test between nodules and thrombus occurrence

The relationship test analysis between nodules and thrombus occurrence was conducted to see whether nodule type is related or correlated with thrombus occurrence. The relationship test used was the Spearman correlation test because the data is ordinal category with ordinal category. The following table shows the relationship test between nodules and thrombus occurrence:

Table 5. Relationship test between nodules and thrombus occurrence

Variable	n	Thrombus			r Spearman	p value
		None	Present only in portal branches	Present in main portal		
Nodul						
Encapsulating	2	2 (100%)	0 (0%)	0 (0%)	0,610	0,000
Simple nodular with extranodular growth	5	5 (100%)	0 (0%)	0 (0%)		
Multinodular confluent	23	15 (65,2%)	5 (21,7%)	3 (13,0%)		
Infiltrative	29	6 (20,7%)	4 (13,8%)	19 (65,5%)		

* stated as having a relationship if $p < 0.05$

Table 5 shows that in the encapsulating nodule type group, all cases, namely 2 subjects (100%), had no thrombus. A similar finding was also seen in the simple nodular with extranodular growth type, where there were 5 cases (100%) without thrombus. In the multinodular confluent type, of the 23 cases found, 15 cases (65.2%) had no thrombus, 5 cases (21.7%) had thrombus in portal branches, and 3 cases (13.0%) had thrombus in the main portal. Meanwhile, in the infiltrative type, which is the most common type with 29 cases, 6 cases (20.7%) had no thrombus, 4 cases (13.8%) had thrombus in portal branches, and the majority, namely 19 cases (65.5%), were found with thrombus in the main portal. Analysis results show a Spearman test p value of 0.000, where $p < 0.05$, meaning there is a statistically significant relationship between nodule type and thrombus occurrence. Based on the correlation coefficient value (r) of 0.610, where the correlation value is positive, indicating that the more aggressive or infiltrative the nodule type, the greater the tendency for thrombus occurrence, especially in the main portal. The correlation coefficient value (r) of 0.610 indicates the strength of the relationship between nodule type and thrombus occurrence falls into the strong relationship category because the r value is in the range of 0.600-0.800.

This finding shows that infiltrative nodule type has the highest risk for thrombus occurrence compared to other nodule types. Thus, this result provides an important picture that nodule growth patterns, especially those that are infiltrative, should be watched out for because they are closely related to thrombus formation.

Analysis of demographic test with thrombus occurrence

Demographic analysis with thrombus occurrence was conducted to see whether demographics in the study, namely gender and age, are related or become confounding/biased with thrombus occurrence. The test used is a comparison test where the Chi Square test for gender because it is nominal categorical data, and ANOVA test for age because age data is stated to be normal. The following table shows the demographic test with thrombus occurrence:

Table 6. Demographic test with thrombus occurrence

Demographics	n	Thrombus			p value
		None	Present only in portal branches	Present in main portal	
Gender					
Male	45	20 (44,4%)	8 (17,8%)	17 (37,8%)	0,558
Female	14	8 (57,1%)	1 (7,1%)	5 (35,7%)	
Age					
Mean ± SD	59	58,79 ± 14,495	58,89 ± 13,290	51,73 ± 7,542	0,106

*stated as significant/becoming confounding/bias if $p < 0.05$

Table 6 presents the results of demographic characteristics with thrombus occurrence in 59 research subjects. Based on gender, in the male group, 20 cases (44.4%) had no thrombus, 8 cases (17.8%) had thrombus in portal branches, and 17 cases (37.8%) had thrombus in the main portal. Meanwhile, in the female group, 8 cases (57.1%) had no thrombus, 1 case (7.1%) had thrombus in portal branches, and 5 cases (35.7%) had thrombus in the main portal. Test results show a p value of 0.558, where p > 0.05, meaning there is no significant difference between gender and thrombus occurrence. Based on age, the mean age of subjects without thrombus was 58.79 ± 14.495 years. The mean age of subjects with thrombus in portal branches was 58.89 ± 13.290 years, while in subjects with thrombus in the main portal it was lower at 51.73 ± 7.542 years. Test results show a p value of 0.106, where p > 0.05, meaning there is no significant difference between age based on thrombus occurrence.

Thus, demographic factors, namely gender and age, are stated to be not significant with thrombus occurrence in this study, so it can be concluded that both variables are not confounding or biasing the relationship between nodules and thrombus occurrence. This finding complements previous results, that thrombus occurrence is more influenced by nodule patterns, especially infiltrative type, compared to subject demographic factors.

Discussion

Patient demographic analysis

Based on gender distribution, from 59 samples, male gender was found more often in 45 samples (76.3%) compared to females in 14 samples (23.7%). Several literature sources show that hepatocellular carcinoma cases are found more often in male patients compared to female patients. This is associated with hepatocellular carcinoma risk factors in male patients being 2 to 4 times higher risk compared to females. Factors such as exposure to risk factors, hormonal differences, and high expression of androgen receptors in males contribute to male dominance in HCC incidence. [28–30]

For descriptive demographic age from 59 samples, the age range was from 30 to 85 years with a median age of 55.0 years, for the mean and standard deviation of age was 56.17 ± 12.438, which means the age description of subjects showed that subject age based on mean falls into middle age/middle adulthood (40-59 years). This is consistent with the information that the young age group (18-39 years) of HCC patients is relatively small, about 9%, while the majority is the 40-74 year age group (about 80%) and the elderly age group ≥75 years about 11%. [31,32]

HCC usually develops against a background of chronic liver disease that has been ongoing for a long time, such as liver cirrhosis due to hepatitis B, hepatitis C, excessive alcohol consumption, or non-alcoholic fatty liver disease. This process takes years, so liver cancer tends to appear in middle to late age, namely 40-70 years.[33] In addition, at this age phase, it reflects a time when the accumulation of genetic mutations and chronic liver cell damage reaches a critical point that allows transformation into cancer. Studies show genetic mutations such as CTNNB1 occur more often in patients aged ≥40 years. HCC is found frequently at ages 40-70 years because chronic pathological processes and gradual accumulation of genetic mutations take years to develop into liver cancer, with the peak of diagnosis usually occurring in that age range.[32]

Sample analysis based on nodule and thrombus assessment

Nodule variable measurement based on 4 categories/criteria, namely: Encapsulating nodular, Simple nodular with extranodular growth, Multinodular confluent, and Infiltrative. While for the thrombus variable based on 3 categories/criteria, namely: None, Present only in portal branches, and Present in main portal. In the nodule variable, most cases were found with infiltrative type, namely 29 cases or 49.2%. Next, multinodular confluent type was found in 23 cases or 39.0%. Simple nodular with extranodular growth type was recorded in 5 cases or 8.5%, while encapsulating type was the least found, namely only 2 cases or 3.4%. Thus, the most dominant nodule pattern in this study was infiltrative type. This can be associated with the research location being a referral center for Eastern Indonesia. Therefore, patients referred tend to be in end-stage condition.

In the thrombus variable, almost half of the subjects had no thrombus, namely 28 cases or 47.5%. Thrombus in portal branches was found in 9 cases or 15.3%, while thrombus in the main portal was found in 22 cases or 37.3%. This shows that although almost half of the subjects did not have thrombus, in cases with thrombus, most were found in the main portal. This is consistent with the theory that thrombus formation usually begins in the portal vein and can sometimes extend to other branches of the portal system such as the splenic vein and mesenteric vein.[34]

Sample analysis based on relationship between nodules and thrombus occurrence

In the encapsulating nodule type group, all cases, namely 2 subjects (100%), had no thrombus. A similar finding was also seen in the simple nodular with extranodular growth type, where there were 5 cases (100%) without thrombus. In the multinodular confluent type, of the 23 cases found, 15 cases (65.2%) had no thrombus, 5 cases (21.7%) had thrombus in portal branches, and 3 cases (13.0%) had thrombus in the main portal. Meanwhile, in the infiltrative type, which is the most common type with 29 cases, 6 cases (20.7%) had no thrombus, 4 cases (13.8%) had thrombus in portal branches, and the majority, namely 19 cases (65.5%), were found with thrombus in the main portal. This finding shows a statistically significant relationship between nodule type and thrombus occurrence, where the correlation value is positive, indicating that the more aggressive or infiltrative the nodule type, the greater the tendency for thrombus occurrence, especially in the main portal. This finding supports the hypothesis that non-smooth tumor margins (in infiltrative type and multinodular confluent type), detected on multiphase CT, are found to correlate with pathological presence and location of microvascular invasion.[35] In addition, Lim et al., 2006 reported that capsule disruption on CT correlates with microvascular invasion ($P<0.001$), and the presence of intact HCC capsule on CT closely correlates with the absence of microvascular invasion. These two points support the correlation between nodule type in hepatocellular carcinoma and the tendency for tumor thrombus occurrence.

Type I nodules, encapsulated nodular, with encapsulated nodule position usually have clear fibrotic capsule margins separating the tumor from surrounding healthy liver tissue. This capsule functions as a physical barrier that limits tumor invasion to surrounding blood vessels, thereby reducing the risk of tumor infiltrating hepatic veins or portal veins to form tumor thrombus. In encapsulated nodular type, the presence of local neovascularization is usually limited to the tumor area, and does not cause invasion into the main vascular system as much as other types that grow diffusely. This reduces the opportunity for the tumor to enter the blood circulation and form thrombus in large blood vessels according to Amin et al.[36]

Simple nodular with extranodular growth type has a relatively localized nodular growth pattern and is sometimes accompanied by limited extranodular growth. Although it has growth areas outside the main nodule, the level of vascular invasion or major blood vessel infiltration is still relatively low compared to other types such as confluent multinodular or infiltrative types which are more aggressive. Studies show that simple nodular type with extranodular growth tends to have better differentiation and not too aggressive cell proliferation rates, so the risk of tumor cells infiltrating blood vessels to form tumor thrombus is lower compared to multinodular and infiltrative types.[37,38]

In multinodular confluent type, several tumor nodules merge to form a larger tumor mass and often have infiltrative growth. This irregular and extensive growth increases the chances of tumor cells infiltrating portal blood vessels or hepatic veins, thereby triggering tumor thrombus formation[39].

Meanwhile, for infiltrative type, this tumor develops in a liver environment that may already have cirrhosis, which causes blood vessel endothelial damage. HCC tumor cells in this type release various pro-inflammatory cytokines such as IL-6 and TNF-α that damage the endothelium and increase blood vessel vulnerability to invasion and thrombosis. The Extracellular Matrix (ECM) remodeling process by cancer-associated fibroblasts and active type 2 macrophages helps tumor penetration into surrounding vascular structures. Increased factors such as VEGF and HIF-1α in tumor hypoxia areas also play a role in vascular invasion and tumor thrombus formation. In addition, the presence of cancer stem cells in this tumor type is also associated with blood vessel invasion and portal thrombus, through expression of cell adhesion molecules such as EpCAM and CD133 that facilitate tumor spread and vascular invasion[39].

Conclusion

Based on research results, it can be concluded that the distribution of hepatocellular carcinoma cases occurs most often in male patients with a prevalence of 76.3% compared to females at 23.7%. In addition, the most common age group in this study was in the 40–59-year age range, which shows that hepatocellular carcinoma is more dominant in productive to early elderly age. Statistical analysis results using Spearman correlation test showed a p value of 0.000 ($p < 0.05$), indicating a statistically significant relationship between nodule type and thrombus occurrence. The correlation coefficient value (r) of 0.610 shows a positive correlation with moderate to strong strength, meaning the more aggressive or infiltrative the nodule type, the greater the tendency for thrombus occurrence, especially in the main portal vein. Meanwhile, analysis results also showed that there is no significant relationship between patient age and thrombus occurrence in hepatocellular carcinoma patients, so age cannot be used as a predictor factor for thrombus occurrence in this study.

This research is a retrospective study with a cross-sectional design, so data collection was only conducted at one specific time. This design has limitations because research results can be influenced by various confounding factors that cannot be fully controlled, such as patient age, hepatitis infection history, lifestyle history, and hepatocellular carcinoma stage when the patient first came to the referral hospital. Another limitation in this study is the relatively limited sample size obtained only in a certain time period. This condition potentially affects the ability to generalize research results to a wider population, so interpretation of findings needs to be done carefully. In addition, the research location conducted at a referral hospital is also a limitation in itself. Patients coming to referral hospitals are generally in more severe disease conditions or have entered advanced stages, so the case characteristics obtained do not fully represent hepatocellular carcinoma patients at early stages.

Based on these research results, it is recommended that future research use a prospective approach so that researchers can control examination variables and confounding factors better, and obtain more comprehensive and accurate data. In addition, the number of research samples should be increased so that the variation of cases obtained is more diverse. With a larger sample size, it is hoped that the distribution of each nodule type can be more balanced so that the analysis of relationships between variables becomes stronger and more representative. Future research is also recommended to develop studies on the correlation of thrombus formation with nodule types in hepatocellular carcinoma patients undergoing abdominal CT scan examination, considering other factors not discussed in this study, such as the relationship of certain biomarkers that have the potential to predict thrombus occurrence.

References

1. Asafo-Agyei, K. O., & Samant, H. (2024).

Hepatocellular carcinoma. 2023 jun 12. StatPearls, Treasure Island (FL): StatPearls Publishing.

2. Janevska, D., Chaloska-Ivanova, V., & Janevski, V. (2015). Hepatocellular carcinoma: risk factors, diagnosis and treatment. *Open Access Macedonian Journal of Medical Sciences*, *3*(4), 732. https://doi.org/10.3889/oamjms.2015.111
3. Baiocchini, A., Grillo, L. R., & Ettorre, G. M. (2022). Pathology of hepatocellular carcinoma. In *Hepatocellular Carcinoma* (pp. 45–52). Springer International Publishing Cham. https://doi.org/10.1007/978-3-031-09371-5_6
4. Zhou, J., Sun, H., Wang, Z., Cong, W., Wang, J., Zeng, M., Zhou, W., Bie, P., Liu, L., & Wen, T. (2020). Guidelines for the diagnosis and treatment of hepatocellular carcinoma (2019 edition). *Liver Cancer*, *9*(6), 682–720. https://doi.org/10.1159/000509424
5. Farazi, P. A., & DePinho, R. A. (2006). Hepatocellular carcinoma pathogenesis: from genes to environment. *Nature Reviews Cancer*, *6*(9), 674–687. https://doi.org/10.1038/nrc1934
6. Martani, I. P., Sitanggang, F., Margiani, N., Widiana, I. G., Asih, M., & Ayusta, I. M. (2022). Correlation of Abdominal CT scan Score and Alpha-fetoprotein Levels in Hepatocellular Carcinoma. *International Journal of Integrated Health Sciences*, *10*(2), 88–93. https://doi.org/10.15850/ijihs.v10n2.2768
7. Rimola, J., Forner, A., Reig, M., Vilana, R., de Lope, C. R., Ayuso, C., & Bruix, J. (2009). Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. *Hepatology*, *50*(3), 791–798. https://doi.org/10.1002/hep.23071
8. Lurje, I., Czigany, Z., Bednarsch, J., Roderburg, C., Isfort, P., Neumann, U. P., & Lurje, G. (2019). Treatment strategies for hepatocellular carcinoma—a multidisciplinary approach. *International Journal of Molecular Sciences*, *20*(6), 1465. https://doi.org/10.3390/ijms20061465
9. Giannelli, G., Koudelkova, P., Dituri, F., & Mikulits, W. (2016). Role of epithelial to mesenchymal transition in hepatocellular carcinoma. *Journal of Hepatology*, *65*(4), 798–808. https://doi.org/10.1016/j.jhep.2016.05.007
10. Pavlovic, N., Rani, B., Gerwins, P., & Heindryckx, F. (2019). Platelets as key factors in hepatocellular carcinoma. *Cancers*, *11*(7), 1022. https://doi.org/10.3390/cancers11071022
11. Abdulloh, A. (2023). Imaging of the Anterior Communicating Artery: Normal and Abnormal Findings Related to Aneurysm. *PHARMACOLOGY, MEDICAL REPORTS, ORTHOPEDIC, AND ILLNESS DETAILS*, *2*(1), 1–7. https://doi.org/10.55047/comorbid.v2i1.753
12. Elsayes, K. M., Kielar, A. Z., Chernyak, V., Morshid, A., Furlan, A., Masch, W. R., Marks, R. M., Kamaya, A., Do, R. K. G., & Kono, Y. (2019). LI-RADS: a conceptual and historical review from its beginning to its recent integration into AASLD clinical practice guidance. *Journal of Hepatocellular Carcinoma*, 49–69. https://doi.org/10.2147/JHC.S186239
13. Lee, Y., Wang, J. J., Zhu, Y., Agopian, V. G., Tseng, H., & Yang, J. D. (2021). Diagnostic criteria and LI-RADS for hepatocellular carcinoma. *Clinical Liver Disease*, *17*(6), 409–413. https://doi.org/10.1002/cld.1075
14. Bolondi, L., Gaiani, S., Celli, N., Golfieri, R., Grigioni, W. F., Leoni, S., Venturi, A. M., & Piscaglia, F. (2005). Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. *Hepatology*, *42*(1), 27–34. https://doi.org/10.1002/hep.20728
15. Rao, P. N. (2014). Nodule in liver: Investigations, differential diagnosis and follow-up. *Journal of Clinical and Experimental Hepatology*, *4*, S57–S62. https://doi.org/10.1016/j.jceh.2014.06.010
16. Colombo, M. (2015). Diagnosis of liver nodules within and outside screening programs. *Annals of Hepatology*, *14*(3), 304–309.
17. Sun, E. X., Shi, J., & Mandell, J. C. (2021). *Core radiology: A visual approach to diagnostic imaging*. Cambridge University Press.
18. Abdulloh, A., & Ni'mah, A. Q. (2023). BI-RADS Classification for Breast Ultrasound: A Review. *Pharmacology, Medical Reports, Orthopedic, and Illness Details*, *2*(2), 67–84.

https://doi.org/10.55047/comorbid.v2i2.840
19. Hennedige, T., & Venkatesh, S. K. (2013). Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring. *Cancer Imaging*, *12*(3), 530. https://doi.org/10.1102/1470-7330.2012.0044
20. Mezale, D., Strumfa, I., Vanags, A., Kalva, A., Balodis, D., Strumfs, B., Fridrihsone, I., Abolins, A., & Gardovskis, J. (2018). Diagnostic algorithm of hepatocellular carcinoma: Classics and innovations in radiology and pathology. *Hepatocellular Carcinoma-Advances in Diagnosis and Treatment*, 17–46.
21. Rafi, M. A. (2024). De-Escalating Intensity and Preserving Outcomes: A Bayesian-ML Network Meta-Analysis of Multimodal Treatment Strategies in HPV-Positive Oropharyngeal Cancer. *PHARMACOLOGY, MEDICAL REPORTS, ORTHOPEDIC, AND ILLNESS DETAILS*, *3*(3), 139–157. https://doi.org/10.55047/comorbid.v3i3.1699
22. Gonvers, S., Martins-Filho, S. N., Hirayama, A., Calderaro, J., Phillips, R., Uldry, E., Demartines, N., Melloul, E., Park, Y. N., & Paradis, V. (2024). Macroscopic Characterization of Hepatocellular Carcinoma: An Underexploited Source of Prognostic Factors. *Journal of Hepatocellular Carcinoma*, 707–719. https://doi.org/10.2147/JHC.S447848
23. Dewi, S. C. R., Arinawati, A., Darmini, D., & Prakoso, D. (2021). Informasi Citra Anatomi Pada Penggunaan Variasi Increment Pemeriksaan Msct Abdomen Irisan Axial Kasus Nodul Hepar. *Jurnal Imejing Diagnostik (Jimed)*, *7*(2), 65–69. https://doi.org/10.31983/jimed.v7i2.7462
24. Asafo-Agyei, K. O., & Samant, H. (2023). Hepatocellular Carcinoma. In *StatPearls.*
25. Kelekis, N. L., Semelka, R. C., Worawattanakul, S., De Lange, E. E., Ascher, S. M., Ahn, I.-O., Reinhold, C., Remer, E. M., Brown, J. J., & Bis, K. G. (1998). Hepatocellular carcinoma in North America: a multiinstitutional study of appearance on T1-weighted, T2-weighted, and serial gadolinium-enhanced gradient-echo images. *AJR. American Journal of Roentgenology*, *170*(4), 1005–1013. https://doi.org/10.2214/ajr.170.4.9530051
26. Choi, B. I., & Lee, J. M. (2010). Advancement in HCC imaging: diagnosis, staging and treatment efficacy assessments: imaging diagnosis and staging of hepatocellular carcinoma. *Journal of Hepato-Biliary-Pancreatic Sciences*, *17*(4), 369–373. https://doi.org/10.1007/s00534-009-0227-y
27. Szklaruk, J., Silverman, P. M., & Charnsangavej, C. (2003). Imaging in the diagnosis, staging, treatment, and surveillance of hepatocellular carcinoma. *American Journal of Roentgenology*, *180*(2), 441–454. https://doi.org/10.2214/ajr.180.2.1800441
28. Nevola, R., Ruocco, R., Criscuolo, L., Villani, A., Alfano, M., Beccia, D., Imbriani, S., Claar, E., Cozzolino, D., & Sasso, F. C. (2023). Predictors of early and late hepatocellular carcinoma recurrence. *World Journal of Gastroenterology*, *29*(8), 1243. https://doi.org/10.3748/wjg.v29.i8.1243
29. Melchor-Ruan, J., Santiago-Ruiz, L., Murillo-Ortiz, B. O., Rivera-Rivera, S., Leal-Herrera, Y. A., Suárez-García, D., Remes-Troche, J. M., Grube, P., Martínez-Mier, G., & Ruiz-García, E. (2024). Characteristics of Hepatocellular Carcinoma by Sex in Mexico: A Multi-Institutional Collaboration. *Diseases*, *12*(10), 262. https://doi.org/10.3390/diseases12100262
30. Hwang, S. Y., Danpanichkul, P., Agopian, V., Mehta, N., Parikh, N. D., Abou-Alfa, G. K., Singal, A. G., & Yang, J. D. (2024). Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment. *Clinical and Molecular Hepatology*, *31*(Suppl), S228. https://doi.org/10.3350/cmh.2024.0824
31. Yang, J. D., Addissie, B. D., Mara, K. C., Harmsen, W. S., Dai, J., Zhang, N., Wongjarupong, N., Ali, H. M., Ali, H. A., & Hassan, F. A. (2019). GALAD score for hepatocellular carcinoma detection in comparison with liver ultrasound and proposal of GALADUS score. *Cancer Epidemiology, Biomarkers & Prevention*, *28*(3), 531–538. https://doi.org/10.1158/1055-9965.EPI-18-0281
32. Ang, C., Shields, A., Xiu, J., Gatalica, Z., Reddy, S., Salem, M. E., Farhangfar, C., Hwang, J.,

Astsaturov, I., & Marshall, J. L. (2017). Molecular characteristics of hepatocellular carcinomas from different age groups. *Oncotarget*, *8*(60), 101591. https://doi.org/10.18632/oncotarget.21353

33. McGlynn, K. A., Petrick, J. L., & El-Serag, H. B. (2021). Epidemiology of hepatocellular carcinoma. *Hepatology*, *73*, 4–13. https://doi.org/10.1002/hep.31288
34. Saito, T., Kunieda, T., Hashimoto, Y., Ishida, M., Maru, N., Utsumi, T., Matsui, H., Taniguchi, Y., Hino, H., & Murakawa, T. (2023). Internal carotid bulb occlusion by a giant thrombus after thoracoscopic left upper lung lobectomy successfully treated with endovascular stenting: a case report. *General Thoracic and Cardiovascular Surgery Cases*, *2*(1), 104. https://doi.org/10.1186/s44215-023-00116-4
35. Yoneda, N., Matsui, O., Kobayashi, S., Kitao, A., Kozaka, K., Inoue, D., Yoshida, K., Minami, T., Koda, W., & Gabata, T. (2019). Current status of imaging biomarkers predicting the biological nature of hepatocellular carcinoma. *Japanese Journal of Radiology*, *37*(3), 191–208. https://doi.org/10.1007/s11604-019-00817-3
36. Amin, S., Shahab, A., Qazi, A. R., Yunus, H., Saeed, L., Khan, A. A., Rehman, M. E. U., & Khan, N. A. (2023). A rare incidence of hepatocellular carcinoma with tumor thrombus extending to the right heart. *Cureus*, *15*(8), e43965. https://doi.org/10.7759/cureus.43965
37. Kanai, T., Hirohashi, S., Upton, M. P., Noguchi, M., Kishi, K., Makuuchi, M., Yamasaki, S., Hasegawa, H., Takayasu, K., & Moriyama, N. (1987). Pathology of small hepatocellular carcinoma. A proposal for a new gross classification. *Cancer*, *60*(4), 810–819. https://doi.org/10.1002/1097-0142(19870815)60:4<810::AID-CNCR2820600417>3.0.CO;2-1
38. Fukutomi, S., Nomura, Y., Nakashima, O., Yano, H., Tanaka, H., Akagi, Y., & Okuda, K. (2017). Evaluation of hepatocellular carcinoma spread via the portal system by 3-dimensional mapping. *HPB*, *19*(12), 1119–1125. https://doi.org/10.1016/j.hpb.2017.08.011
39. Galasso, L., Cerrito, L., Termite, F., Mignini, I., Esposto, G., Borriello, R., Ainora, M. E., Gasbarrini, A., & Zocco, M. A. (2024). The molecular mechanisms of portal vein thrombosis in hepatocellular carcinoma. *Cancers*, *16*(19), 3247. https://doi.org/10.3390/cancers16193247