**RESEARCH PAPER**

# Correlation Between Platelet Count in Patients with Hepatocellular Carcinoma and LI-RADS Criteria Based on Abdominal CT Scan Examinations at Dr. Soetomo Regional General Hospital, Surabaya

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**ABSTRACT**

Hepatocellular carcinoma (HCC) is a primary liver malignancy with high mortality rates, while the Liver Imaging Reporting and Data System (LI-RADS) is used to determine the probability of HCC based on radiological imaging characteristics. Platelets are known to play a role in tumor progression, but their relationship with LI-RADS classification remains unclear. This study aims to determine the relationship between platelet count and LI-RADS classification in HCC patients. This study is a retrospective observational analytical study of 56 HCC patients who underwent abdominal CT-scan examination at Dr. Soetomo General Hospital Surabaya from January to December 2023. LI-RADS classification was determined based on multiphasic CT-scan, while platelet data were obtained from blood tests performed at most 10 days before or after radiological examination. Relationship analysis was performed using Spearman correlation test. The results showed that the majority of subjects were male (83.9%) with a mean age of 52.25 ± 9.92 years. Most patients were categorized as LI-RADS 5 (87.5%) and had normal platelet counts (85.7%). Correlation test showed no significant relationship between platelet count and LI-RADS classification ($p = 0.269$), and no meaningful relationship was found between platelets and main LI-RADS features such as arterial phase hyperenhancement, washout, and enhancing capsule ($p > 0.05$). The conclusion of this study shows that platelet count does not correlate with LI-RADS classification in HCC patients and therefore cannot be used as a predictive indicator of HCC probability level based on radiological imaging, and further research is needed considering confounding factors such as liver function, portal hypertension, and cytokine profile.

**Keywords**: *Hepatocellular carcinoma; LI-RADS; platelets; abdominal CT-scan; liver imaging.*

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignant tumor of hepatocytes.[1] HCC is currently the fourth leading cause of cancer-related deaths worldwide and the sixth most common cancer diagnosis. The incidence of HCC has increased in various populations in recent decades with 841,000 new cases and 782,000 deaths annually, with the highest incidence rates still reported in Southeast Asia and Sub-Saharan Africa.[2,3] HCC is a highly lethal liver tumor due to the lack of chemopreventive drugs in high-risk populations, delayed detection, frequent presentation in late stages, and high recurrence rates with currently available treatments. Therefore, its prognosis is considerably poor compared to other tumor diseases.[2]

HCC diagnosis is performed with a multidisciplinary approach such as clinical, radiological, and laboratory with or without liver biopsy.[4] Radiologically, HCC diagnosis can be established in patients at risk for HCC based on multiphase CT or MRI without histological confirmation.[5] Imaging features suggesting HCC include nonrim arterial phase hyperenhancement (APHE), washout in portal venous and/or delayed phase, enhancing capsule, minimum size of 1 cm, and growth threshold of ≥50% in ≤6 months. Based on the presence/absence of these main features, as well as several additional features (e.g., restricted diffusion, corona enhancement, mosaic architecture, etc.), liver lesions can be determined by their LI-RADS criteria which reflect the likelihood of HCC.[6]

Platelets are one of the blood components produced in the bone marrow and play an important role in blood clotting processes [7]. Normal platelet counts in adults and children are approximately 150,000 - 450,000/microL, but the normal range may vary according to clinical laboratories. Thrombocytosis (>450,000/microL) is classified into 2 criteria: primary thrombocytosis and secondary thrombocytosis. Primary thrombocytosis is caused by abnormal platelet production in bone marrow progenitor cells *(polycythemia vera)*.[8] Secondary thrombocytosis or

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reactive thrombocytosis is an increase in platelets due to external causes such as bacterial infections, tuberculosis, inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease), neoplastic diseases, acute bleeding, hemolytic anemia, post-splenectomy or asplenia, as well as iron deficiency.[9]

The relationship between thrombocytosis and malignancy has been known for a century. This is especially seen in malignancies of the lung, colon, gynecology, kidney and is also associated with primary liver malignancy.[10] According to Arslan and Coskun (2005), the specific mechanism of thrombocytosis in malignancy is still speculative and several hypotheses have been proposed regarding this. In recent years, humoral mediators are thought to play an important role in the pathogenesis of thrombocytosis which is considered as the body's response to malignant tissue. Excessive amounts of cytokines have been found to be associated with thrombocytosis in malignancy.[10] Therefore, thrombocytosis is associated with larger tumor size and conversely thrombocytopenia is often associated with small-sized tumors.[11]

Based on recent research by Lu et al (2020), it was proven that platelets act as important factors in HCC proliferation and contribute to distant metastasis, possibly through glycoprotein (GP) IIb, GPIb-IX-V and p-selectin adhesion receptor.[12] Platelets are also a source of several HCC growth factors involved in tumor interaction, tumor growth, tumor angiogenesis, and protection of tumor cells from immune responses.[13] This suggests that anti-platelet therapy may prevent or slow HCC progression.[11] A number of platelet count (PLT)-containing predictive models have been established to identify HCC risk and evaluate prognosis or recurrence in patients after curative resection in early-stage HCC.[12]

Determination of HCC diagnosis radiologically using LI-RADS category is less familiar in Indonesia. HCC determination is more often done clinically, through laboratory and radiological examinations but without LI-RADS criteria. Platelet examination is commonly performed routinely and simply along with other complete blood test examinations. There is additional prognostic benefit by combining these two parameters. A study is needed to determine the correlation between LI-RADS and platelet values in patients with identified hepatocellular carcinoma (HCC). This study aims to determine the relationship between LI-RADS and platelet values that has not been discussed in previous studies. This aims to identify which LI-RADS features are most consistent with increased platelet counts to determine diagnosis and prognosis of liver malignancy with simple laboratory tests.

## MATERIALS AND METHODS

This study is an observational analytical study with a retrospective approach. The target population in this study was patients with hepatocellular carcinoma who underwent abdominal CT-scan examination. The accessible population was hepatocellular carcinoma patients who performed abdominal CT-scan examination at the Radiology Installation of Dr. Soetomo General Hospital in the period from January to December 2023. Research samples were taken from the accessible population that met the inclusion criteria.

The sample size in this study was calculated using the sample size formula for correlation tests, with a type I error rate (α) of 0.05 and a type II error of 0.05. The standard Zα value used was 1.96 and Zβ was 1.64, while the expected correlation coefficient based on the research by Martani et al. (2022) was 0.460. Based on these calculations, a minimum sample size of 56 research subjects was obtained. This number is considered to have met the research power requirement of 95%.[14]

Inclusion criteria in this study included subjects at high risk for hepatocellular carcinoma, such as patients with liver cirrhosis or hepatitis B and/or C virus infection with or without cirrhosis. In addition, subjects must have a diagnosis of hepatocellular carcinoma established through biopsy results, typical radiological features, or atypical radiological features accompanied by an increase in alpha-fetoprotein (AFP) levels above 400 ng/ml. Subjects must also undergo contrast-enhanced abdominal CT-scan examination and have complete medical records, especially platelet values examined at most 10 days before or after CT-scan examination.

Exclusion criteria in this study included patients under 18 years of age, patients with incomplete MDCT images in three phases (arterial, venous, and delayed), and patients with a history of certain diseases such as polycythemia vera, hemolytic anemia, or chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. In addition, patients with a history of post-splenectomy or asplenia, as well as patients with bacterial infections indicated by increased leukocyte counts, were also excluded from this study.

This study was conducted at the Radiology Installation of Dr. Soetomo General Hospital Surabaya from January 2023 to December 2024. Research variables analyzed included LI-RADS category in hepatocellular carcinoma based on abdominal CT-scan results and patient platelet values.

Research instruments used included a 128-slice Philips CT-scan machine with serial number 145872 and tube MRC 880 (device number 989000086371) used for abdominal radiology examinations. In addition, platelet value measurements were performed using Sysmex Automated Hematology Analyzer type XN-3000 located at the Diagnostic Center Building (GDC) of Dr. Soetomo General Hospital Surabaya.

Data collection in this study was carried out through measurement and evaluation of abdominal CT-scan results performed by a radiology specialist consultant in the

abdomen field with approximately five years of work experience. CT-scan examination data were then collected and systematically arranged into a case report form (CRF) as a basis for data processing.

After all data were collected, analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25.0 software. Data analysis included descriptive analysis and quantitative analysis. In descriptive analysis, examination results were grouped based on subject characteristics, namely age, gender, and research variables, then frequency and distribution were calculated. Furthermore, quantitative analysis was performed through bivariate tests to determine the relationship between LI-RADS category and platelet levels in hepatocellular carcinoma patients. The statistical test used was the Spearman nonparametric test because the data analyzed were ordinal scale, both on LI-RADS and platelet variables. The p value was considered statistically significant if $p < 0.05$ with a confidence level of 95%. Statistical analysis results were presented in table form, while the correlation coefficient value denoted by ρ (rho) was used to show the strength and direction of the relationship between the two variables studied.

Regarding research ethics aspects, the author has submitted a research ethics approval application to the Ethics Committee of the Faculty of Medicine, Airlangga University Surabaya/Dr. Soetomo General Hospital Surabaya before the research was conducted.

## RESULTS AND DISCUSSION

### Descriptive Research Data

From 56 samples, descriptive or overview of research data was examined including gender, age, hepatitis B & C, size (largest dimension), arterial phase, washout, enhancing capsule, platelets, and LI-RADS where data are presented in frequency and percentage form for categorical data and range, median, mean and standard deviation values for numerical data:

**Table 1. Descriptive Data**

| | Frequency (%) | Range (Median) | Mean ± SD |
|---|---|---|---|
| **Gender** | | | |
| Male | 47 (83,9%) | | |
| Female | 9 (16,1%) | | |
| **Age** | | 26 – 75 (53,00) | 52,25 ± 9,922 |
| **Hepatitis B** | | | |
| Negative | 5 (8,9%) | | |
| Positive | 51 (91,1%) | | |
| **Hepatitis C** | | | |
| Negative | 50 (89,3%) | | |
| Positive | 6 (10,7%) | | |
| **Size (Largest Dimension)** | | | |
| < 20 mm | 0 (0%) | | |
| ≥ 20 mm | 56 (100%) | | |
| **Arterial Phase** | | | |
| Iso/Hypoenhancement | 5 (8,9%) | | |
| Atorial Phase non-rim Hyperenhancement | 51 (91,1%) | | |
| Washout | | | |
| Present | 49 (87,5%) | | |
| Absent | 7 (12,5%) | | |
| **Enhancing Capsule** | | | |
| Present | 3 (5,4%) | | |
| Absent | 53 (89,5%) | | |
| **Platelets** | | | |
| Thrombocytopenia | 4 (7,1%) | | |
| Normal Platelets | 48 (85,7%) | | |
| Thrombocytosis | 4 (7,1%) | | |
| **LI-RADS** | | | |
| Definitely Benign (LIRADS 1) | 0 (0%) | | |
| Probably Benign (LIRADS 2) | 0 (0%) | | |
| Intermediate Probability (LIRADS 3) | 4 (7,1%) | | |
| Probably HCC (LIRADS 4) | 3 (5,4%) | | |
| Definitely HCC (LIRADS 5) | 49 (87,5%) | | |

Based on descriptive results, the majority of research subjects were male (83.9%) with an age range of 26–75 years and average age of 52.25 years. Most patients had positive hepatitis B status (91.1%) and negative hepatitis C (89.3%). All respondents showed lesion size ≥ 20 mm indicating dominance of cases with large tumor size. Radiologically, the most frequently found characteristics were arterial phase non-rim hyperenhancement pattern (91.1%) and presence of washout (87.5%), while enhancing capsule was rarely found (5.4%). From a hematological perspective, most patients had normal platelet counts (85.7%). Based on LI-RADS classification, the majority of cases were classified as Definitely HCC (87.5%), indicating that the research population was dominated by patients with characteristic hepatocellular carcinoma features and high radiological diagnostic certainty.

**Descriptive and Demographic Testing Based on Platelets**

Descriptive and demographic testing based on platelets examines whether there is a relationship between demographic data including gender, age, hepatitis B & C, size (largest dimension), with platelet events including thrombocytopenia, normal platelets, thrombocytosis. The following is descriptive and demographic testing based on platelets:

**Table 2.** Descriptive and Demographic Testing Based on Platelets

| Demography | n | Thrombocytopenia | Normal Platelets | Thrombocytosis | p value |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Male | 47 | 4 (8,5%) | 41 (87,2%) | 2 (4,3%) | 0,119 |
| Female | 9 | 0 (0%) | 7 (77,8%) | 2 (22,2%) | |
| **Age** | | | | | |
| Mean ± SD | 56 | 59,00 ± 16,021 | 51,69 ± 9,159 | 52,25 ± 12,971 | 0,440 |
| **Hepatitis B** | | | | | |
| Negative | 5 | 1 (20,0%) | 4 (80,0%) | 0 (0%) | 0,431 |
| Positive | 51 | 3 (5,9%) | 44 (86,3%) | 4 (7,8%) | |
| **Hepatitis C** | | | | | |
| Negative | 50 | 3 (6,0%) | 43 (86,0%) | 4 (8,0%) | 0,512 |
| Positive | 6 | 1 (16,7%) | 5 (83,3%) | 0 (0%) | |
| **Size (Largest Dimension)** | | | | | |
| < 20 mm | 0 | 0 (0%) | 0 (0%) | 0 (0%) | - |
| ≥ 20 mm | 56 | 4 (7,1%) | 48 (85,7%) | 4 (7,1%) | |

*Declared significant if p value < 0.05

Table 2 shows that the distribution of platelet counts (thrombocytopenia, normal, and thrombocytosis) has no significant relationship with demographic characteristics of research subjects. Based on gender, both males and females were dominated by the normal platelet group, with a p value = 0.119 (p>0.05). Mean age in the three platelet groups also showed no significant difference (p = 0.440). Hepatitis B and hepatitis C status were not significantly related to variations in platelet counts, with p values of 0.431 and 0.512 respectively. All patients had lesion size ≥ 20 mm so analysis of the relationship between lesion size and platelet count could not be performed. Overall, these results indicate that demographic factors, including gender, age, hepatitis B and C status, and lesion size, do not act as confounding factors for platelet events in research subjects.

**Descriptive and Demographic Testing Based on LI-RADS**

Descriptive and demographic testing based on LI-RADS examines whether there is a relationship between demographic data including gender, age, hepatitis B & C, size (largest dimension), with LI-RADS including Definitely Benign, Probably Benign, Intermediate Probability, Probably HCC, and Definitely HCC. The following is descriptive and demographic testing based on LI-RADS:

**Table 3.** Descriptive and Demographic Testing Based on LI-RADS

| Demo-graphy | n | Definitely Benign (LIRADS 1) | Probably Benign (LIRADS 2) | Intermediate Probability (LIRADS 3) | Probably HCC (LIRADS 4) | Definitely HCC (LIRADS 5) | p value |
|---|---|---|---|---|---|---|---|
| **Gender** | | | | | | | |
| Male | 47 | 0 (0%) | 0 (0%) | 4 (8,5%) | 3 (6,4%) | 40 (85,1%) | 0,465 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Female | 9 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 9 (100%) | |
| **Age** | | | | | | | |
| Mean ± SD | 56 | 0 ± 0,0 | 0 ± 0,0 | 59,50 ± 7,141 | 51,00 ± 6,083 | 51,73 ± 10,165 | 0,290 |
| **Hepatitis B** | | | | | | | |
| Negative | 5 | 0 (0%) | 0 (0%) | 1 (20,0%) | 0 (0%) | 4 (80,0%) | 0,449 |
| Positive | 51 | 0 (0%) | 0 (0%) | 3 (5,9%) | 3 (5,9%) | 45 (88,2%) | |
| **Hepatitis C** | | | | | | | |
| Negative | 50 | 0 (0%) | 0 (0%) | 3 (6,0%) | 3 (6,0%) | 44 (88,0%) | 0,542 |
| Positive | 6 | 0 (0%) | 0 (0%) | 1 (16,7%) | 0 (0%) | 5 (83,3%) | |
| **Size (Largest Dimension)** | | | | | | | |
| < 20 mm | 0 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | - |
| ≥ 20 mm | 56 | 0 (0%) | 0 (0%) | 4 (7,1%) | 3 (5,4%) | 49 (87,5%) | |

*Declared significant if p value < 0.05

Table 3 shows that LI-RADS classification in research subjects has no significant relationship with demographic characteristics. Based on gender, both males and females were dominated by the Definitely HCC category, with a p value = 0.465 (p>0.05). Mean age in the Intermediate Probability, Probably HCC, and Definitely HCC categories also showed no significant difference (p = 0.290). Hepatitis B and hepatitis C status were not significantly related to LI-RADS classification, with p values of 0.449 and 0.542 respectively. All patients had lesion size ≥ 20 mm so analysis of the relationship between lesion size and LI-RADS classification could not be performed. Overall, these results indicate that demographic factors, including gender, age, hepatitis B and C status, and lesion size, do not act as confounding factors for LI-RADS classification in research subjects.

**Analysis of Relationship Test Between Platelets and LI-RADS Classification**

Analysis of relationship test between platelets and LI-RADS examines whether there is a relationship between platelet events including thrombocytopenia, normal platelets, thrombocytosis with LI-RADS including Definitely Benign, Probably Benign, Intermediate Probability, Probably HCC, and Definitely HCC. The following is the test of platelets with LI-RADS:

**Table 4.** Relationship Test Between Platelets and LI-RADS

| | n | Definitely Benign (LIRADS 1) | Probably Benign (LIRADS 2) | Intermediate Probability (LIRADS 3) | Probably HCC (LIRADS 4) | Definitely HCC (LIRADS 5) | r | p value |
|---|---|---|---|---|---|---|---|---|
| **Platelets** | | | | | | | | |
| Thrombo-cytopenia | 4 | 0 (0%) | 0 (0%) | 1 (25,0%) | 0 (0%) | 3 (75,0%) | | 0,269 |
| Normal Platelets | 48 | 0 (0%) | 0 (0%) | 3 (6,3%) | 3 (6,3%) | 42 (87,5%) | 0,150 | |
| Thrombo-cytosis | 4 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 (100%) | | |

* Declared significant if p value < 0.05

Table 4 shows the results of analysis of the relationship between platelet count and LI-RADS classification in research subjects. In the group with thrombocytopenia (4 people), there were no cases in the benign category, but there was 1 person (25.0%) in the Intermediate Probability category and 3 people (75.0%) in the Definitely HCC category. In the group with normal platelets (48 people), 3 people (6.3%) were in the Intermediate Probability category, 3 people (6.3%) were in the Probably HCC category, and the majority, 42 people (87.5%), were in the Definitely HCC category. Meanwhile, in the group with thrombocytosis (4 people), all (100%) were in the Definitely HCC category without any cases in other categories.

Correlation test results using the Spearman test because ordinal data with ordinal showed a p value of 0.269 (p >0.05) indicating that there is no significant relationship between platelet count and LI-RADS classification. These results illustrate that variations in platelet count (thrombocytopenia, normal, or thrombocytosis) are not significantly related to the level of LI-RADS classification.

**Table 5. Relationship Between Platelet Count and LI-RADS**

| | n | Thrombocytopenia | Normal Platelets | Thrombocytosis |
|---|---|---|---|---|
| **LI-RADS** | | | | |
| Intermediate Probability (LI-RADS 3) | 4 | 1 (25,0%) | 3 (75,0%) | 0 (0%) |
| Probably HCC (LI-RADS 4) | 3 | 0 (0%) | 3 (100%) | 0 (0%) |
| Definitely HCC (LI-RADS 5) | 49 | 3 (6,1%) | 42 (85,8%) | 4 (8,1%) |

Table 5 shows the majority of samples in this study belonged to the LI-RADS 5 (definitely HCC) category, totaling 49 samples. In this group, most patients had platelet counts within normal range (85.8%), while thrombocytosis was only found in 8.1% and thrombocytopenia in 6.1% of samples. In the LI-RADS 3 (intermediate probability) group, a relatively high proportion of normal platelets was found (75.0%), with a small portion of thrombocytopenia (25.0%) and no thrombocytosis found. Meanwhile, all LI-RADS 4 (probably HCC) samples showed platelet counts within normal limits (100%). These findings indicate that in lesions with lower or not yet definitive HCC probability, platelet count disorders are also not dominant, either in the form of thrombocytopenia or thrombocytosis.

**Analysis of Relationship Test Between Platelets and LI-RADS Feature Components**

Analysis of relationship test between platelets and LI-RADS feature components examines whether there is a relationship between platelet events including thrombocytopenia, normal platelets, thrombocytosis with arterial phase, washout and enhancing capsule. The following is the test of platelets with LI-RADS feature components:

**Table 6.** Test of Platelets with LI-RADS Feature Components

| LI-RADS Features | n | Thrombocytopenia | Normal Platelets | Thrombocytosis | p value |
|---|---|---|---|---|---|
| **Arterial Phase** | | | | | |
| Iso/Hypoenhancement | 5 | 1 (20,0%) | 4 (80,0%) | 0 (0%) | 0,431 |
| Atorial Phase non-rim Hyperenhancement | 51 | 3 (5,9%) | 44 (86,3%) | 4 (7,8%) | |
| **Washout** | | | | | |
| Present | 49 | 3 (6,1%) | 42 (85,7%) | 4 (8,2%) | 0,565 |
| Absent | 7 | 1 (14,3%) | 6 (85,7%) | 0 (0,0%) | |
| **Enhancing Capsule** | | | | | |
| Present | 3 | 0 (0%) | 3 (100%) | 0 (0%) | 0,768 |
| Absent | 53 | 4 (7,5%) | 45 (84,9%) | 4 (7,5%) | |

* Declared significant if p value < 0.05

Table 6 shows that there is no significant relationship between platelet count and main radiological features in the LI-RADS system, namely arterial phase, washout, and enhancing capsule. In the arterial phase, most cases in both iso/hypoenhancement and arterial phase non-rim hyperenhancement patterns were dominated by patients with normal platelets, and statistical test results showed a p value = 0.431 (p>0.05). In the washout feature, the majority of cases with or without washout were also dominated by normal platelets, with a p value = 0.565 (p>0.05). Meanwhile, in the enhancing capsule feature, all cases showing the presence of capsule had normal platelets, but statistically it was still not significant with a p value = 0.768 (p>0.05). Overall, these results confirm that variations in platelet count are not related to the appearance of main radiological features in LI-RADS classification, so patient platelet status does not play a role in determining radiological patterns in the LI-RADS system.

## DISCUSSION

**Demographic and Clinical Characteristics of Samples**

From the 56 samples, the majority were male, totaling 47 people (83.9%), with 9 people (16.1%) being female. Respondent ages ranged from 26 to 75 years, with a median of 53 years. Sample distribution showed that the majority of patients were male (83.9%), with the 41-60 year age group being the most numerous, consistent with

demographic analysis indicating higher prevalence of liver nodules in males within the productive age range.[15] Most samples showed positive results for Hepatitis B (91.1%), while 10.7% were positive for Hepatitis C. The high prevalence of Hepatitis B in this research population is consistent with the fact that chronic Hepatitis B infection is a major risk factor for the development of liver nodules and hepatocellular carcinoma.[15]

**Radiological Findings and LI-RADS**

In terms of lesion size, all 56 samples (100%) had the largest dimension ≥ 20 mm with an average size of 16.9 cm. Observed radiological features showed that 91.1% of samples had Arterial Phase non-rim Hyperenhancement in the arterial phase, and 87.5% showed washout. The presence of non-rim hyperenhancement in the arterial phase and washout phenomenon are significant radiological features for diagnosing hepatocellular carcinoma (Elsayes et al., 2019). LI-RADS classification showed that most samples (87.5%) fell into the Definitely HCC category (LIRADS-5). The rest were distributed into Intermediate Probability (LIRADS 3) (7.1%) and Probably HCC (LIRADS 4) (5.4%), with no cases of Definitely Benign (LIRADS 1) or Probably Benign (LIRADS 2).

**Analysis of Relationships Between Variables**

Statistical analysis results using Chi-Square test showed that demographic characteristics such as gender, age, Hepatitis B, and Hepatitis C had no significant relationship with LI-RADS classification. This indicates that these demographic factors do not become confounding factors in platelet events. Furthermore, this study also concluded that main radiological features in LI-RADS classification, namely arterial phase, washout, and enhancing capsule, showed no significant relationship with platelet count (p value > 0.05).

In this study, most patients with hepatocellular carcinoma (HCC) categorized as LI-RADS 4–5 had platelet counts within normal limits, without considering the presence or absence of cirrhosis. Most HCC patients with LI-RADS 4-5 category had platelet counts within normal limits, this finding shows that platelet levels may not directly correlate with tumor aggressiveness indicators assessed through imaging using the LI-RADS system. Although thrombocytosis has been reported as a paraneoplastic phenomenon in several types of cancer, including HCC, this phenomenon is likely influenced by various conflicting mechanisms in the liver micro-environment and the complexity of pathophysiology in patients with chronic liver disease and HCC. This confirms that platelet homeostasis regulation in HCC patients is multifactorial and does not always directly correlate with tumor aggressiveness indicators assessed through LI-RADS imaging. The following are several theories of platelet homeostasis regulation in HCC patients consistent with this research results:

**1) Balancing Pathophysiological Effects on Platelet Homeostasis**

In patients with chronic liver disease, platelet counts are influenced by two opposing mechanisms, namely platelet-increasing factors originating from hepatocellular carcinoma (HCC) tumor and platelet-decreasing factors due to impaired liver function. Several types of malignancy, including HCC, can cause thrombocytosis as part of paraneoplastic syndrome, which occurs when tumor cells produce cytokines such as interleukin-6 (IL-6) or thrombopoietin in excessive amounts.[16] Increased IL-6 plays a role in stimulating megakaryocytes in bone marrow to increase platelet production, thereby contributing to increased platelet counts in some HCC patients.[17]

Conversely, in chronic liver disease, especially cirrhosis which is a major risk factor for HCC, there are several mechanisms that cause decreased platelet counts. Portal hypertension that often accompanies cirrhosis can cause splenomegaly, which leads to increased platelet sequestration in the spleen so that platelet counts in peripheral circulation decrease and cause thrombocytopenia.[18,19] This thrombocytopenia condition is also often found in HCC patients who have cirrhosis as an underlying disease.[2] In addition, the liver is the main organ producing thrombopoietin, which is a hormone that plays an important role in stimulating platelet production in bone marrow.[17] In patients with significant liver damage, the liver's ability to produce thrombopoietin can decrease, thus also contributing to low platelet counts.[16] Thus, the balance between platelet-increasing effects by tumor activity and platelet-decreasing due to liver dysfunction determines the platelet profile in patients with HCC and chronic liver disease.

Therefore, normal platelet counts in HCC patients with high LI-RADS can be explained as a balance between platelet-decreasing effects due to chronic liver disease (portal hypertension, splenic sequestration, decreased TPO) and potential platelet-increasing effects induced by tumor. In this case, platelet-decreasing effects may be strong enough to offset tumor-induced platelet production, so platelet counts remain within normal range.

This research results show variations in platelet counts in hepatocellular carcinoma (HCC) patients, which can be understood through the concept of balance between two pathophysiological forces: tumor-induced platelet-increasing factors and platelet-decreasing factors due to chronic liver disease. Research findings support that thrombocytosis and thrombocytopenia conditions in HCC patients can be explained by the dominance of one of these mechanisms.

**a. Thrombocytosis Group**

In the thrombocytosis group, the research found that all samples showed no cirrhosis, and only 1 of 4 samples had

portal hypertension, which was caused by portal vein thrombosis. This condition illustrates that platelet-decreasing factors due to chronic liver disease (such as portal hypertension, splenic sequestration, and decreased TPO production) are not dominant in this group. The absence of cirrhosis is very important, considering cirrhosis is the main cause of portal hypertension and decreased TPO production.[17,18] With the weakening of these platelet-decreasing factors, platelet-increasing mechanisms originating from tumor become more prominent. HCC tumors are known to produce cytokines such as interleukin-6 (IL-6) or thrombopoietin, which can increase megakaryocyte stimulation and platelet production.[16,17] Therefore, in patients without cirrhosis and without portal hemodynamic disorders, tumor paraneoplastic effects are more clearly visible, resulting in thrombocytosis.

**b. Thrombocytopenia Group**

Conversely, in the thrombocytopenia group, although cirrhosis was not found, there was dominance of platelet-decreasing factors. Research showed that 3 of 4 samples experienced portal hypertension due to portal vein thrombosis, and 2 of them were accompanied by splenomegaly. Both conditions are important mechanisms in decreasing platelet counts. Portal hypertension causes increased pressure in the portal system, which leads to splenomegaly and increased platelet sequestration in the spleen.[19] Although there is no cirrhosis, the presence of portal thrombosis provides a similar effect on portal pressure and platelet sequestration.

With the strength of these mechanisms, tumor platelet-increasing effects are not strong enough to offset the decrease in platelet counts. This explains why some HCC patients still experience thrombocytopenia although theoretically tumors can increase platelet production.

**2) Interpretation of Platelet Homeostasis Based on Mechanism Balance**

Overall, research results show that platelet counts in HCC patients are determined by the balance between two pathophysiological forces:

- Platelet-increasing effects through IL-6 or thrombopoietin secretion by tumor.
- Platelet-decreasing effects through portal hypertension, splenic sequestration, and decreased TPO production due to liver dysfunction.

In the thrombocytosis group, platelet-increasing forces are more dominant, due to the absence of cirrhosis and low splenic involvement. In the thrombocytopenia group, platelet-decreasing forces are greater, especially through portal hypertension and splenomegaly mechanisms due to portal thrombosis.

These findings are consistent with the theory that normal or abnormal platelet counts in HCC patients are the result of dynamic balance between processes that increase and decrease platelets.[2,16,17]

**3) Molecular Heterogeneity Between Tumors and Cytokine Production**

HCC is known to have significant molecular heterogeneity. This means that not all HCC tumors have the same genetic characteristics or gene expression profiles. This heterogeneity can cause variations in the tumor's ability to produce cytokines that drive thrombopoiesis. Tumors that appear very vascular and meet LI-RADS 5 criteria on imaging, which reflect radiologically aggressive behavior, do not necessarily intrinsically produce cytokines such as IL-6 or TPO in sufficient amounts to cause systemic thrombocytosis.[20] Paraneoplastic thrombocytosis phenomenon may be more related to certain molecular subsets of HCC.

In this study, further analysis regarding tumor genetic profile or gene expression could not be performed due to molecular data limitations. This limitation restricts the research's ability to link clinical and radiological findings with underlying molecular mechanisms, especially regarding cytokine production affecting thrombopoiesis.

Therefore, further research with molecular and genomic approaches, including analysis of IL-6, TPO expression, and related inflammatory pathways, is greatly needed to clarify the relationship between HCC molecular heterogeneity, imaging characteristics, and platelet count changes. Integration of molecular data with radiological and clinical findings is expected to provide more comprehensive understanding of paraneoplastic mechanisms in HCC.

**4) Good Liver Function**

Normal platelet counts in HCC patients can also be an indicator of relatively preserved liver function and/or milder degree of portal hypertension. In HCC with better liver function, TPO production may not be too disrupted, so there is more "room" for tumor to trigger slight platelet increase without causing obvious thrombocytosis, or simply to keep platelet counts within normal limits despite tumor activity. This condition can be found in certain populations, for example in patients with HCC due to Hepatitis B who may develop without obvious cirrhosis or in early-stage cirrhosis.[14] Although most HCC cases develop from cirrhosis, some cases can emerge without obvious cirrhosis, especially in HBV patients.[20]

Evaluation of liver dysfunction in patients with hepatocellular carcinoma (HCC) is an important component in clinical assessment, because underlying liver function not only affects prognosis, but also determines therapy choices and interpretation of radiological findings. In general, laboratory examinations recommended to assess liver function and reserve include parameters of synthesis function, excretion, and hepatocellular integrity. The most frequently used

parameters are aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) as markers of hepatocellular injury, total and direct bilirubin as indicators of bile excretion function, as well as serum albumin and prothrombin time/INR as reflections of liver synthesis function.[21]

In this study, not all samples had complete and uniform laboratory data according to recommended liver function parameters. Some samples only had partial laboratory examinations, so evaluation of liver dysfunction degree could not be performed comprehensively. This condition becomes a research limitation, because variations in laboratory data completeness potentially affect interpretation of relationships between liver function, tumor characteristics, and other clinical parameters. These laboratory data limitations also restrict this research's ability to perform liver function stratification objectively using standardized scoring systems. Therefore, this research results need to be interpreted with caution, especially in drawing conclusions regarding liver dysfunction influence on radiological findings and other clinical parameters studied.

Further research is expected to use prospective design with standardization of liver function laboratory examinations, so that relationships between liver dysfunction degree, hepatocellular carcinoma characteristics, and clinical outcomes can be analyzed more accurately and statistically significantly.

**5) Large Tumor Size**

Large HCC generally shows central necrosis, which occurs due to imbalance between tumor cell metabolic needs and inadequate vascular supply in the central part of the lesion. This necrosis process not only affects tumor structural and metabolic integrity, but also changes the cytokine milieu in surrounding tissue. These changes can impact systemic cytokine signaling pathways that play roles in thrombopoiesis and platelet homeostasis.

In normal physiological conditions, several proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-11 (IL-11), and interleukin-3 (IL-3) have important roles in stimulating thrombopoietin (TPO) production by hepatocytes. TPO is the main regulator of megakaryocyte proliferation and differentiation in bone marrow, which ultimately determines platelet counts in circulation. Several in vitro studies show that IL-6 can increase TPO mRNA expression in hepatoma cells, strengthening the functional relationship between the IL-6-TPO axis in liver tissue.

In large HCC generally included in high LI-RADS category (LI-RADS 4-5), central necrosis is often found as a typical histopathological feature. This necrosis can cause decreased viability of tumor cells and immune cells in peritumoral area, thereby reducing proinflammatory cytokine secretion such as IL-6 and IL-11. Decreased stimulation of these cytokines theoretically can reduce TPO synthesis so platelet value increase does not occur and hepatocytes that still function well can maintain normal thrombopoiesis.[22]

Overall, findings that HCC with high LI-RADS 4-5 category have platelet counts within normal limits show that platelet homeostasis regulation in HCC patients is multifactorial and does not always directly correlate with tumor aggressiveness indicators based on imaging. This is due to balancing effects between platelet-decreasing factors due to chronic liver disease (portal hypertension, splenic sequestration, decreased thrombopoietin production by diseased liver) and potential platelet-increasing effects from tumor, as well as HCC molecular heterogeneity in producing thrombopoiesis-triggering cytokines. Even large tumor size with central necrosis can cause decreased proinflammatory cytokines and thrombopoietin synthesis, thereby contributing to normal platelet counts. Therefore, LI-RADS and platelet counts represent two different biological dimensions of HCC, where imaging focuses on local tumor vascular phenotype, while platelets reflect complex interactions between liver function, spleen, systemic inflammatory processes and potential paraneoplastic effects from tumor.

In this study, both in thrombocytosis and thrombocytopenia sample groups, qualitative assessment found that tumor necrosis degree exceeded 50% of tumor volume. Therefore, further research with quantitative approach is needed to objectively calculate necrosis-to-tumor ratio. This quantitative approach is expected to provide more accurate picture of the relationship between tumor necrosis extent and platelet status, and allow statistically stronger correlation or association analysis.

## CONCLUSION

Based on research results, it can be concluded that there is no correlation between platelet values in hepatocellular carcinoma patients with LI-RADS criteria. LI-RADS score characterization showed that most samples, totaling 87.5% (49 people), were in the Definitely HCC category (LI-RADS 5). Meanwhile, 7.1% (4 people) were in the Intermediate Probability category (LI-RADS 3) and 5.4% (3 people) in the Probably HCC category (LI-RADS 4), with no cases found in the Definitely Benign (LI-RADS 1) or Probably Benign (LI-RADS 2) categories. In addition, analysis results also showed that there is no significant relationship between platelet values in patients with hepatocellular carcinoma. In the thrombocytopenia group, 25.0% (1 person) was in LI-RADS 3 category and 75.0% (3 people) were in LI-RADS 5 category. In the group with normal platelets, 6.3% (3 people) were in LI-RADS 3 category, 6.3% (3 people) were in LI-RADS 4 category, and the majority of 87.5% (42 people) were in LI-RADS 5 category. Meanwhile, all subjects in the thrombocytosis group (100% or 4 people) were in LI-RADS 5 category

without distribution in other categories. As a suggestion, further research is recommended to examine the relationship between platelets and hepatocellular carcinoma by controlling various confounding factors, such as liver cirrhosis, portal hypertension, splenomegaly, and hepatocellular carcinoma with extensive necrosis. In addition, combination of liver function assessment, portal hypertension degree, and cytokine profile also needs to be considered to obtain more comprehensive understanding of the complex relationship between platelets and hepatocellular carcinoma.

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