Neutrophil-to-lymphocyte ratio as a predictive marker for portal vein thrombosis in hepatocellular carcinoma

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Abstract. Portal vein thrombosis (PVT) is a prevalent complication and a poor prognostic factor in patients with hepatocellular carcinoma (HCC). The present study aimed to evaluate the predictive value of the neutrophil-to-lymphocyte ratio (NLR) for PVT in patients diagnosed with HCC. From February, 2024 to May, 2025, a cross-sectional study was conducted on 197 patients with HCC. The study population was segregated into two groups as follows: One with PVT (30%) and one without PVT (70%). The NLR was determined using peripheral blood cells at the time of diagnosis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal NLR cut-off for predicting PVT. Multivariable logistic regression was performed to assess the independent association between NLR and PVT, adjusting for tumor size and α-fetoprotein (AFP). The optimal NLR cut-off found was 2.817, which yielded an area under the ROC curve (AUC) of 0.695, a sensitivity of 68.4% and a specificity of 66.4%. In multivariate analysis, an elevated NLR ≥2.817 was independently associated with an increased risk of PVT [odds ratio (OR), 4.31; 95% confidence interval (CI), 1.98-9.42; P<0.001] after adjusting for tumor size and AFP. Therefore, NLR is a significant independent predictor of PVT in patients with HCC.

Introduction

Liver cancer is the sixth most prevalent form of cancer worldwide and the fourth most common cause of cancer-related mortalities (1). Portal vein thrombosis (PVT) is a prevalent complication in patients with hepatocellular carcinoma (HCC), affecting ~40% of cases (2). PVT is a poor prognostic factor that increases mortality rates by reducing blood flow in the liver, resulting in portal hypertension, ascites, hepatic encephalopathy and liver failure (3). PVT also facilitates the dissemination of tumors throughout the liver parenchyma (1).

The pathogenesis of PVT in HCC is highly intricate and involves a combination of multiple factors. Venous stasis, endothelial injury and hypercoagulability comprise Virchow's triad. The velocity of portal blood flow is diminished in HCC as a result of portal hypertension, tumor compression or the loss of normal liver tissue structure. This stasis facilitates the formation of thrombi. Furthermore, the tumor directly damages the endothelial tissue and initiates a coagulation response by invading the portal vein wall. The synthesis of natural anticoagulants (protein S, protein C and antithrombin) is reduced in patients with HCC due to liver injury, while cancer cells overproduce procoagulant factors, such as tissue factors, resulting in increased activation of the coagulation system (4). Currently, chronic inflammation frequently plays a role in the pathogenesis of thrombus formation. Numerous inflammatory mediators, including TNF-α, interleukin (IL)-6, interferon-γ, transforming growth factor β, IL-17, IL-9, IL-1β and chemokines, such as CXC motif chemokine ligand (CXCL) 8/CXCL1 and C-C motif chemokine ligand 2, are released by cancer cells, all of which contribute to endothelial injury (5). Neutrophils are activated by inflammatory cytokines, which facilitate their adhesion to endothelial cells, promote inflammation and platelet aggregation and result in the formation of thrombus (6-8). Neutrophils are crucial in the inflammatory response and, as a result, serve a substantial role in the formation of thrombus. Obtained from a peripheral blood cell count, the neutrophil-to-lymphocyte ratio (NLR) is a simple index that indicates the immune and inflammatory functions of the body. Researchers have investigated it as a possible predictive biomarker for different types of cancer, such as HCC (1,9). Nevertheless, there is a lack of studies examining the predictive relevance of NLR in predicting thrombosis in patients with HCC, although some researchers have mentioned the role of NLR in predicting the prognosis of HCC (10). The objective of the present study

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was to assess the predictive value of NLR in the recognition of PVT in patients with HCC.

Patients and methods

Subjects and research design. The present cross-sectional investigation was performed at Bach Mai Hospital (Hanoi, Vietnam) from February, 2024 to May, 2025. Patients who were ≥18 years of age, had a first-time confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases (AASLD) guidelines (11) and had not received treatment were included in the study. The study excluded patients who were on medication that affected their white blood cell count, had a history of hematological disease or had an infection. The patients were divided into two different groups as follows: Patients diagnosed with PVT through computed tomography or magnetic resonance imaging scans comprised group 1. The second group consisted of patients who did not have PVT. The study protocol was approved by the Institutional Review Board of Hanoi Medical University (no. 1063/GCN-HMUIRB) in January, 2024.

Data collection. Prior to commencing treatment, peripheral blood cell indices were obtained, which included the number of white blood cells, neutrophils, lymphocytes, monocytes and platelets, as well as the concentration of hemoglobin. Coagulation parameters, including fibrinogen, D-dimer, prothrombin time (PT) and activated partial thromboplastin time (APTT) were also collected. The study also collected data on the following: Disease [age, sex, etiology of HCC, body mass index (BMI)], liver function [Child-Pugh, Barcelona Clinic Liver Cancer classification (BCLC)] (12,13), α-fetoprotein (AFP) and tumor characteristics [size, Tumor-Node-Metastasis staging system (TNM)] (14).

Statistical analysis. The following two categories were compared: Non-thrombotic and PVT. The qualitative variables (sex, etiology of HCC, Child-Pugh, BCLC and TNM) were analyzed using χ^2 or Fisher's exact test. The quantitative variables (hemoglobin concentration; white blood cell, neutrophil, lymphocyte, monocyte and platelet counts; NLR, fibrinogen and D-dimer concentrations; AFP, tumor size and BMI) were analyzed using independent samples t-tests or Mann-Whitney U tests, depending on their normal or non-normal distribution. To determine whether the data follow a normal distribution or not, the Kolmogorov-Smirnov test was used; in the event that the P-value of the test was >0.05, the assumption of normal distribution data was accepted. The Youden index and receiver operating characteristic (ROC) analysis was used to determine the most appropriate NLR threshold for distinguishing between groups with and without PVT. Logistic regression analysis was implemented to assess how well NLR predicted PVT in patients with HCC. Multivariate regression analysis of NLR was performed with adjustment for AFP and tumor size to determine the independent significance of NLR in predicting the risk of PVT in patients with HCC. The AFP threshold of ≥400 ng/ml was selected based on clinical evidence of poor predictive relevance with increased risk of recurrence or progression (15,16). The tumor size threshold of ≥3 cm was used to separate risk groups, based on the standard for small and large HCC, to determine the effect of tumor size on thrombotic risk and survival (17). SPSS 22.0 software (IBM Corp.) was employed to performed all analyses, with a value of P<0.05 considered to indicate a statistically significant difference.

Results

Patient characteristics. The present study included 197 patients diagnosed with HCC. The prevalence of PVT was 30%. The patients were predominantly male, the mean age of the non-thrombotic group was higher compared with that of the PVT group (P=0.011), and the mean total tumor volume (TTV) of the PVT group was higher than that of the non-thrombotic group (P<0.001) (Table I). The causes of HCC, which include alcohol consumption, hepatitis B and C virus infection, cirrhosis and BMI, did not exhibit any significant differences between the groups (all P>0.05). Significant differences were observed between the group with PVT and the group without PVT in terms of the HCC stage, according to Child-Pugh, TNM and BCLC (Table I).

Peripheral blood cells and biomarkers. As demonstrated in Table II, the PVT group had elevated neutrophil counts, NLR, total bilirubin, AFP, aspartate aminotransferase, alanine aminotransferase, PT-international normalized ratio (INR) and D-dimer levels; however, lymphocyte counts and albumin levels were diminished in comparison with the non-thrombotic group (all P<0.05). No significant differences were observed between the two groups as regards platelet count, white blood cell count, fibrinogen and APTT (all P>0.05) (Table II).

ROC curve analysis for PVT predictors based on NLR. The ROC curve analysis of NLR for predicting the occurrence of PVT in patients with HCC revealed an area under the curve of 69.5% with a P-value of <0.001 (Fig. 1 and Table III). The ideal threshold value of NLR, determined by the Youden index, was 2.817, exhibiting a sensitivity of 68.4% and a specificity of 66.4%.

As demonstrated in Table IV, in the univariate analysis, characteristics associated with thrombosis occurrence included NLR ratio >2.817, AFP concentration ≥400 ng/ml and tumor size ≥3 cm (all P<0.05). The multivariate logistic regression results indicated that the model was statistically significant (χ^2=46.066; P<0.001). The model included three statistically significant independent variables: NLR ratio ≥2.817 [odds ratio (OR), 4.31; 95% confidence interval (CI), 1.98-9.42; P<0.001], AFP levels ≥400 ng/ml (OR, 3.78; 95% CI, 1.74-8.23; P<0.001) and tumor size ≥3 cm (OR, 11.19; 95% CI, 1.41-88.73; P=0.022). A tumor size ≥3 cm was the most significant predictor, elevating the risk of thrombosis by ~11-fold relative to the cohort with smaller tumors. This suggests that indicators of inflammation (NLR) and progression of tumors (AFP and size) significantly contribute to the mechanism of thrombus formation in patients.

Discussion

Numerous studies have illustrated the notable role of the systemic inflammatory process in the pathogenesis of

Table I. Baseline characteristics of the patients with HCC.

Characteristic	Thrombosis (PVT), n=60	No thrombosis, n=137	P-value
Age in years, mean ± SD	56.72±9.18	61.16±10.21	**0.011**
Sex, n (%)			
Male	53 (88.3)	119 (86.9)	0.775
Female	7 (11.7)	18 (13.1)	
Alcohol abuse, n (%)			
Yes	14 (23.3)	19 (14)	0.106
No	46 (76.7)	117 (86)	
HBV, n (%)			
Yes	47 (78.3)	91 (66.4)	0.093
No	13 (21.7)	46 (33.6)	
HCV, n (%)			
Yes	2 (3.3)	8 (5.9)	0.726
No	58 (96.7)	128 (94.1)	
Cirrhosis, n (%)			
Yes	27 (45)	53 (38.7)	0.406
No	33 (55)	84 (61.3)	
Child Pugh, n (%)			
A	35 (59.3)	112 (82.4)	**0.002**
B	19 (32.2)	21 (15.4)	
C	5 (8.5)	3 (2.2)	
TNM, n (%)			
IA	0 (0)	11 (8)	**<0.001**
IB	2 (3.3)	41 (29.9)	
II	0 (0)	22 (16.1)	
IIIA	0 (0)	21 (15.3)	
IIIB	26 (43.3)	8 (5.8)	
IVA	25 (41.7)	26 (19)	
IVB	7 (11.7)	8 (5.8)	
BCLC, n (%)			
0	0 (0)	8 (5.8)	**<0.001**
A	0 (0)	35 (25.5)	
B	0 (0)	58 (42.3)	
C	57 (95)	33 (24.1)	
D	3 (5)	3 (2.2)	
TTV in cm^3, median (range)	211.3 (5-1863)	41.35 (0.5-1436.7)	**<0.001**
BMI, mean ± SD	21.2±2.37	22.17±2.71	0.061

Values in bold font indicate statistically significant differences (P<0.05). BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PVT, portal vein thrombosis; SD, standard deviation; TNM, Tumor Node Metastasis; TTV, total tumor volume.

thrombosis. According to mouse model experiments, neutrophils were observed to modulate angiogenesis and tumor growth (18). The formation of a thrombus is facilitated by the activation of endothelial cells, platelets and leukocytes during the inflammatory process (19). In addition to secreting cytokines that attract immune cells such as neutrophils and monocytes, activated endothelial cells express P-selectin, which stimulates the adhesion of leukocytes and platelets. Clusters of these cells are formed and adhere to endothelial cells, which are essential components of blood clots (20). Through neutrophil extracellular traps (NETs), neutrophils facilitate the formation of thrombus (20). Furthermore, NETs stimulate the coagulation process by attracting coagulation factors, including factor XIIa, which adhere to fibrin and von Willebrand factor. This results in the recruitment of red blood cells and platelets to the site of thrombus formation (21). Numerous studies have also established an association between systemic inflammation and cancer. The tumor induces the formation of new blood

Table II. Levels of peripheral blood cell and biomarker in the patients with HCC.

Factor	Thrombosis (PVT)	No thrombosis	P-value
Hemoglobin, g/l, mean ± SD	131.8±24.42	139 (53-165)	0.071
Platelet count, 10^9/l, median (range)	188 (54-582)	193.37±94.57	0.183
WBC, 10^9/l, median (range)	7.01 (3.13-15.99)	6.4 (2.02-15.3)	0.101
Neu, 10^9/l, median (range)	4.5 (1.38-13.6)	3.54 (0.98-12.8)	**0.01**
Lymphocyte, 10^9/l, mean ± SD	1.37±0.54	1.8(0.51-4.07)	**0.004**
NLR, median (range)	3.81 (0.78-15.6)	2.34 (0.83-16.8)	**<0.001**
Total bilirubin, μmol/l, median (range)	18.2 (10.5-191.7)	10.85 (3.5-278)	**<0.001**
Creatinine, μmol/l, median (range)	75 (42-171)	77 (36-262)	0.342
Albumin, g/l, median (range)	36.8 (23-47)	37.46±5.5	**0.04**
AST, U/l, median (range)	106 (26-523)	48 (14-834)	**<0.001**
ALT, U/l, median (range)	54 (9-439)	41 (9-562)	**0.014**
AFP, ng/ml, median (range)	2135 (2.2-121000)	72.3 (1.3-121000)	**<0.001**
Fibrinogen, g/l, mean ± SD	3.23±1	3.17±0.99	0.492
PT-INR, median (range)	1.09 (0.92-2.37)	1.03 (0.86-1.91)	**0.012**
APTT sec, mean ± SD	34.28±5.22	33.2(26.8-51.1)	0.436
D-Dimer, ng/ml FEU, median (range)	2123 (179-9552)	854 (128-11015)	**<0.001**

Values in bold font indicate statistically significant differences (P<0.05). PVT, portal vein thrombosis; AFP, α-fetoprotein; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FEU, fibrinogen equivalent units; NLR, neutrophil-to-lymphocyte ratio; Neu, neutrophil; PT, prothrombin time; SD, standard deviation; WBCs, white blood cells.

Table III. ROC parameters and optimal cut-off of NLR for distinguishing the risk of PVT.

AUC	P-value	Cut-off	Sensitivity	Specificity
69.5	<0.001	2.817	68.4	66.4

PVT, portal vein thrombosis; AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.

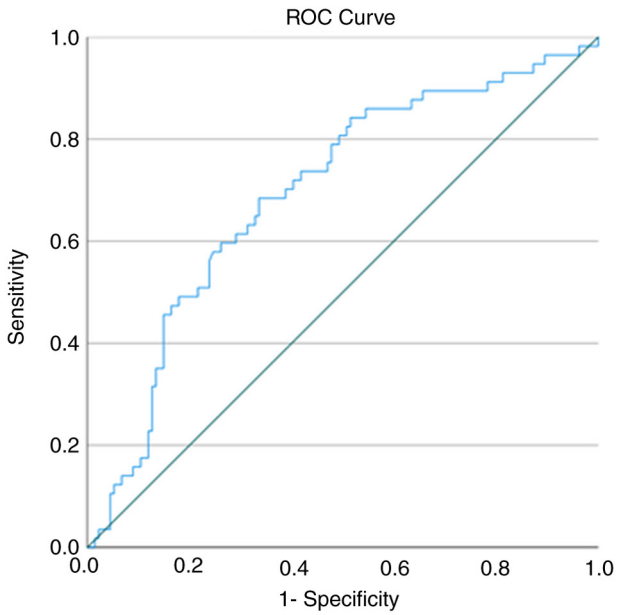

Figure 1. ROC curve analysis of the neutrophil-to-lymphocyte ratio for predicting the occurrence of portal vein thrombosis. ROC, receiver operator characteristic.

vessels, DNA damage and the inhibitory effect of apoptosis by increasing the production of cytokines and inflammatory mediators (22-24). Consequently, the process of systemic inflammation inextricably links the mechanisms of thrombus formation and cancer. Consequently, inflammatory markers can predict the risk of thrombosis in patients with cancer. NLR is a non-specific inflammatory marker that is indicative of the interaction between neutrophils and lymphocytes during inflammation. A high neutrophil count and a lower lymphocyte count are indicative of a higher neutrophil count. A systemic inflammatory process is indicated by an increase in the number of neutrophils, whereas a reduction in the number of lymphocytes suggests a state of reduced immune response (25). Therefore, an elevated NLR may suggest a higher risk of thrombosis in patients with cancer.

Currently, systemic treatment methods for patients with HCC have undergone notable changes with the emergence of immunotherapy regimens combining anti-angiogenic drugs. Regimens such as atezolizumab combined with bevacizumab have become first-line options for patients with advanced HCC, gradually replacing sorafenib monotherapy, with marked improvements in response rates and survival times (26). In addition, recent guidelines on HCC treatment emphasize combined local-regional and systemic therapy, individualized based on tumor burden, liver function and vascular invasion (27). In this context, PVT has become an increasingly crucial factor, not only reflecting the advanced stage of the disease, but also directly affecting the efficacy and safety of

Table IV. Logistic regression analysis for predicting PVT.

	Univariate analysis			Multivariate analysis		
Factor	P-value	OR	95% CI	P-value	OR	95% CI
NLR ≥2.817	<0.001	4.285	2.207-8.321	<0.001	4.31	1.98-9.42
AFP ≥400	<0.001	5.375	2.715-10.643	<0.001	3.78	1.74-8.23
Tumor size ≥3 cm	0.003	20.427	2.725-153.125	0.022	11.19	1.41-88.73

PVT, portal vein thrombosis; AFP, α-fetoprotein; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.

both local interventions and systemic regimens containing anti-VEGF components. An elevated NLR in patients with PVT (28) may be indicative of a tumor microenvironment that promotes vascular invasion and thrombus formation by stimulating thrombogenesis and inflammation (29). The present study demonstrated that patients with HCC and PVT had a much higher NLR compared with those without thrombosis. Multivariate analysis confirmed that NLR ≥2.817 increased the risk of PVT after adjusting for other risk factors, such as AFP and tumor size.

Numerous studies have demonstrated that NLR is a straightforward, cost-effective and user-friendly inflammatory marker that has been assessed as a predictive instrument for the risk of venous thromboembolism in patients with cancer (30,31,32). The NLR has been shown to be higher in a venous thromboembolism group with cancer compared with in a group without cancer (33). In a study involving 271 hospitalized patients with venous thromboembolism, Qian *et al* (34) demonstrated that the presence of an elevated NLR is a predictor of venous thromboembolism in patients with breast cancer following treatment. NLR is a predictor of response to anticoagulant treatment in patients with lung cancer with thrombosis, as demonstrated in the study conducted by Go *et al* (35). The predictive value of NLR in patients with HCC has been demonstrated in a number of studies, which have demonstrated its ability to predict treatment response, disease-free survival and overall survival (36-39). Several predictive ratings for survival time and treatment response in patients with HCC also include NLR (40,41). The predictive value of NLR in patients with HCC is the primary focus of these studies, with only a small number of studies examining the predictive ability of PVT.

AFP is a traditional tumor marker in HCC, which not only reflects tumor burden but is also related to the degree of invasion, growth and thrombosis risk (39). A high AFP level is an independent predictive factor the risk of metastasis and recurrence and is also associated with thrombosis, especially when HCC is accompanied by increased vascular invasion (42,43). A large tumor size is an indicator of a high tumor burden, often accompanied by an increased risk of vascular invasion, particularly of the portal vein, and is therefore directly related to the incidence of thrombosis in HCC (44). Although PVT is a prognostic factor in patients with HCC, the ability to predict the likelihood of PVT can assist physicians in the implementation of early thromboprophylaxis treatment strategies for patients, particularly those with HCC who have an evident tendency towards hypercoagulability (45). Applying the NLR to predict the risk PVT in patients with HCC will help physicians plan for closer imaging surveillance in high-risk groups. This approach will also assist in selecting appropriate systemic treatment regimens, considering the risk of thrombosis associated with anti-VEGF drug therapies. Furthermore, combining NLR, AFP and tumor size could potentially serve as a predictive model for PVT in patients with HCC; however, more large-scale prospective studies are required to validate this model. In addition, impaired liver function (increased bilirubin, decreased albumin) is a factor associated with a higher risk of thrombosis and a worse prognosis (46). Prolonged PT (INR) and elevated D-dimer levels in patients with PVT are also indicative of the activation of the coagulation system, which suggests that fibrin formation and disintegration are ongoing. This hypercoagulable state is consistent with reports of hypercoagulable syndrome in HCC with vascular invasion.

The present study had certain limitations, which should be mentioned. The sample size of the PVT group was small, less than half that of the non-thrombotic group. The present study was a cross-sectional study; therefore, the non-thrombotic group was not followed-up. The authors could not assess whether thrombotic progression occurred in this group.

In conclusion, the present study demonstrates an association between the incidence of PVT in patients with HCC and NLR. The occurrence of PVT is independently associated with an elevated NLR. The value of NLR in preventing thrombosis in patients with HCC remains an unresolved matter. Further research is required in the future to ascertain the optimal NLR threshold for the prevention, diagnosis and treatment of thrombosis, as well as the effective use of this index.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

All authors (TTMN, CPP and MPV) conceived and designed the study. TTMN participated in data collection and processing. TTMN, MPV and CPP participated in data analysis and interpretation. All authors participated in the literature search and wrote the manuscript. All authors have read and approved the final manuscript. TTMN and MPV confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was approved by The Institutional Review Board of Hanoi Medical University approved study number 1063/GCN-HMUIRB. Written informed consent was obtained from all participants prior to enrollment in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that have no competing interests.

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