The Value of Preoperative Neutrophil to Lymphocyte Count Ratio (NLR) in Assessing the Prognosis of Postoperative Patients with Non-B non-C Hepatocellular Carcinoma

wei chen (chenw47@mail.sysu.edu.cn)
Sun Yat-Sen University https://orcid.org/0000-0002-6444-1724
Xiao-ping Tan
Guangzhou Medical University Second Affiliated Hospital
ping fu
Jiangxi Provincial People's Hospital
Shou-wei Jia
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center

Research Article

Keywords: Hepatocellular carcinoma, non-B non-C-HCC, Neutrophil to Lymphocyte Ratio (NLR), Prognosis

Posted Date: April 26th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1513372/v1

Abstract

Background: The prognostic impact of the preoperative neutrophil to lymphocyte ratio (NLR) in patients with non-B, non-C hepatocellular carcinoma (NBNC-HCC) who undergo radical resection is unclear. This study elucidates the prognostic value of NLR in patients undergoing radical resection for NBNC-HCC.

Methods: A total of 212 patients who were treated at the Cancer Center of Sun Yat-sen University from January 1998 to December 2007 were included in this study, and all patients underwent liver tumour resection and had postoperative pathological confirmation of HCC. The 212 patients were divided into four groups according to their NLR and HBsAg. The clinicopathologic and survival characteristics of the patients in Group 4 were compared with those in Groups 1-3.

Results: There were statistically significant differences in age, drinking, body mass index (BMI), diabetes, metabolic syndrome, ALT, AST, tumour size, and secondary tumour ($P<0.05$) between Group 1 (NBNC-AFP(-) vs. B-AFP(+)). The univariate analysis showed that NLR, BMI, drinking, AST, tumour size, secondary tumour and portal violation ($P<0.05$) were factors affecting the disease free survival (DFS) in postoperative HCC patients. A Cox multivariate regression analysis showed that tumour size and secondary tumour ($p<0.05$) were independent factors influencing DFS after surgery. The univariate analysis showed that BMI, AST, tumour size, secondary tumour and portal violation ($p<0.05$) were factors that affected both DFS and OS in NBNC-NLR (-)-HCC patients after surgery, and in addition, the multifactor analysis using a Cox model showed that NLR, secondary tumour and BMI ($p<0.05$) were independent influences on the postoperative DFS in patients with NBNC-NLR (-)-HCC. The Kaplan–Meier survival analysis showed that the NBNC-NLR(-)-HCC patients had the highest rate of DFS among the four patient groups ($p<0.05$). The 1-, 3-, 5- and 10-year DFS rates for the NBNC-NLR(-)-HCC patients were 85.6%, 68.5%, 43.5% and 34.8%, respectively. The NBNC-NLR(-)-HCC patients had a higher postoperative DFS than the B-NLR(+)-HCCNBNC-NLR(+)-HCC and B-NLR(-)-HCC patients ($p<0.05$). The DFS rates at 1, 3, 5 and 10 years after surgery were 85.6%, 68.5%, 43.5% and 34.8% for the NBNC-NLR (-)-HCC group, respectively.

Conclusion: The preoperative NLR is a valid prognostic indicator for patients with non-B non-C-HCC undergoing radical resection.

Background

Hepatocellular carcinoma (HCC) is the 3rd most common cancer worldwide and the most common cause of cancer-related death[1-3]. The incidence of HCC in the United States has increased by approximately 80% over the past 20 years, and 50% of the new cases of HCC are associated with hepatitis C virus, although the aetiology of 15-50% of cases remains unclear[4]. At the same time, the incidence of nonalcoholic fatty liver disease (NAFLD) is increasing. Recent studies have identified NAFLD as a cause of HCC, particularly as a manifestation in cases of nonviral hepatitis B and hepatitis C virus-associated

hepatocellular carcinoma (NBNC-HCC)[5]. Radical hepatectomy is the main treatment modality for patients with HCC. However, the outcome after radical hepatectomy in patients remains unsatisfactory.

Systemic inflammation is strongly associated with the development and progression of cancer and has previously been shown to be an independent predictor of tumour prognosis[6-8]. Classical inflammatory markers that are derived from blood samples, such as the neutrophil to lymphocyte ratio (NLR), have been identified as prognostic markers for certain tumours, including prostate, oesophageal, colon and liver cancers [9-13]. However, a review of the literature revealed that there are currently no studies that have assessed the prognostic value of NLR in patients with NBNC-HCC undergoing radical resection. Therefore, we selected 99 patients with NBNC-HCC and a random sample of 113 patients with B-HCC (HBsAg-positive HCVAb-negative B-HCC). We studied the clinical characteristics and prognostic features of NBNC-NLR(-)-HCC and explored the relationship between NLR, the level of HBsAg, and the survival and prognosis of patients with HCC by various analysis methods.

Patients And Methods

Study Population

This study was conducted from the records of 2591 patients who underwent HCC resection at the Cancer Center of Sun Yat-sen University from January 1998 to December 2007. Inclusion Criteria: All patients were treated via surgical resection of the liver tumours, and the postoperative pathological results confirmed HCC. Ninety-nine patients with NBNC-HCC were screened, and 113 patients were randomly selected from the remaining non-NBNC-HCC patients to serve as a control group. Due to the small number of patients with hepatitis C virus-associated HCC who were identified at screening (n=8 cases), they were not included in this study for analysis. The 212 patients were divided into four groups based on the alpha-fetoprotein (AFP) and hepatitis B surface antigen (HBsAg) positivity (NLR≤2.63 was used as the negative criterion in this study): NBNC-NLR(-)-HCC group ((HBsAg negative HCVAb negative NLR negative, 52 patients), NBNC-NLR(+)-HCC group ((HBsAg negative HCVAb-negative NLR-positive, 47 patients in total), B-NLR(+)-HCC group (HBsAg-positive HCVAb-negative NLR-positive, 63 patients in total) and B-NLR(-)-HCC group (HBsAg-positive HCVAb-negative NLR-negative, 60 patients in total).

Follow-up Information

A total of 212 patients with HCC were included in this study. Blood tests and abdominal imaging, including abdominal ultrasound, enhanced CT or magnetic resonance imaging (MRI), were performed at regular intervals of 3-6 months for two years after surgery. The serum and imaging tests were then performed 6 months thereafter for follow-up. All patients with HCC were staged using the American Joint Committee on Cancer (AJCC) 8th edition staging system. Data on routine blood tests, liver function and methaemoglobin levels were collected within one week before surgery. The clinicopathological characteristics of the patients were also collected, including age at diagnosis, sex, tumour size and number of tumour nodules. NLR was defined as the absolute number of neutrophils divided by the

absolute number of lymphocytes. The study was approved by the Ethics Committee of Jiangxi Provincial People's Hospital. Informed consent was obtained from all patients.

Statistical Analyses

The relationship between NLR and the clinicopathologic variables of patients with HCC was analysed through the X^2 test. The overall survival (OS) rates and disease-free survival (DFS) were analysed using the Kaplan–Meier (KM) method and were compared using the log-rank test. The independent risk factors associated with survival in HCC patients were assessed using multifactorial Cox regression analysis. P values <0.05 were considered statistically significant. SPSS 11.0 was used for the statistical analysis.

Results

Clinical Pathological Characteristics of NBNC-NLR (-)-HCC Patients

Ninety-nine patients with NBNC-HCC were screened from 2591 patients, and the patients NBNC-HCC represented 3.8% of all patients. According to the ROC curve, an NLR of 2.63 was used as the cut-off value, and the patients were divided into a high group (NLR>2.63; n=47, 47.14%) and a low group (NLR≤2.63; n=52, 52.52%). To compare the clinicopathological characteristics of the NBNC-NLR(-)-HCC group with those of the other three groups, the differences were compared using the chi-square test (Table 1). There were statistically significant differences in age, drink, BMI, diabetes, metabolic syndrome, ALT, AST, tumor size, and secondary tumor (P<0.05) between the Group 1 (NBNC-AFP(-) vs. B-AFP(+)). There were statistically significant differences in age, BMI, metabolic syndrome, AST, tumour size and portal invasion in the NBNC-NLR(-)-HCC patients compared to the NBNC-NLR(+)-HCC patients. In addition, the number of patients who underwent postoperative treatment in the different groups is shown in Figure 2.

DFS of the NBNC-NLR(-)-HCC Patients

The univariate analysis of all patients in this study showed that the factors affecting DFS after surgery in patients with HCC were NLR, BMI, drinking, AST, tumour size, secondary tumour and portal invasion (p<0.05) (Table 2). After introducing statistically significant indicators from the univariate analysis into the Cox model multifactor analysis, it was shown that tumour size (p=0.045) and secondary tumour (P=0.001) were independent influencing factors for DFS after surgery (Table 3). The univariate analysis of the NBNC-NLR(-)-HCC patients in this study showed that NLR, BMI, AST, tumour size, secondary tumour and portal vein invasion were factors influencing DFS (p<0.05) (Table 4).

The Kaplan–Meier analysis showed that the NBNC-NLR(-)-HCC patients had a significantly higher DFS than the other groups. The 1-year DFS rates of the patients in the NBNC-NLR(+)/(-)-HCC and B-NLR(+)/(-)-HCC groups were 42.3%, 85.6%, 33.1%, and 51.5%, and the 3-year DFS rates were 32.2%, 68.5%, 30.3%, and 35.9%, respectively. In the three case–control groups, the NBNC-NLR (-)-HCC group was significantly different from the B-NLR (+)-HCC, NBNC-NLR (+)-HCC, and B-NLR (-)-HCC groups in terms of DFS

(P<0.001, P=0.002, P=0.001). The data showed that the DFS rates of the NBNC-NLR(-)-HCC patients at 1, 3, 5 and 10 years were 85.6%, 68.5%, 43.5% and 34.8%, respectively (Table 6).

OS of the NBNC-NLR (-)-HCC Patients

The univariate analysis of all 212 HCC patients in this study showed that in terms of OS, the factors affecting OS after surgery in patients with HCC were BMI, AST, tumour size, secondary tumour and portal invasion (p<0.05) (Table 2). The multivariate Cox regression analysis revealed that BMI, tumour size and portal invasion were independent factors affecting OS after surgery for HCC (Table 3). The univariate analysis of the 52 NBNC-NLR (-)-HCC patients in this study showed that BMI, AST, tumour size, secondary tumour and portal invasion were factors influencing the postoperative OS (P<0.05) (Table 4). A multifactorial analysis using a Cox model showed that BMI was an independent factor influencing OS after surgery in patients with NBNC-NLR (-)-HCC (Table 5).

The 1-year OS rates for patients in the four populations of NBNC-NLR (+)/(-)-HCC and B-NLR(+)/(-)-HCC were 64.5%, 56.9%, 58.9%, 81.2%, respectively; the 3-year OS rates were 40.1%, 50.8%, 41.4%, 58.2%, respectively; and the 5-year OS rates were 30.6%, 46.5%, 36.0%, 52.2%, respectively. There were significant differences in OS in the three case–control groups for the NBNC-NLR (-)-HCC group compared with the B-NLR (+)-HCC, NBNC-NLR(+)-HCC, and B-NLR(-)-HCC groups, and the p values were P=0.311, P=0.486, and P=0.383, respectively.

Discussion

NBNC-HCC is an aggressive disease with a high recurrence and mortality rate even after surgical resection, and both human and financial losses are common in clinical practice[14-16]. NLR is a relatively easy-to-obtain laboratory index that can be obtained without additional expensive laboratory testing equipment and methods. Therefore, its value should be studied jointly by various disciplines, and it should be further combined with other prognostic information to better guide clinicians in developing more rational individualized treatment plans for patients' conditions, which can hopefully also provide some hints for the future direction of basic experimental research on NBNC-HCC.

There is growing evidence that chronic inflammation has an integral role in tumorigenesis, development and progression[17]. High NLR levels are associated with poorer survival and can be used as a biomarker for the prognosis of *patients with different types of cancers,* such as HCC, stomach cancer, breast cancer and colorectal cancer (CRC) [18-21]. However, studies on the prognostic value of NLR in patients undergoing radical resection for NBNC-HCC have not been reported. Therefore, in light of these findings, we evaluated for the first time the predictive role of the preoperative NLR in the prognosis of patients undergoing radical hepatectomy for NBNC-HCC.

The NLR thresholds in previous studies have fluctuated widely, from 1.505 to 5.0. Many studies chose 2.81 as the NLR threshold [22-25]. In this study, we drew an ROC curve with a cut-off value of 2.63, which is very close to the commonly used NLR cut-off value of 2.81. After the analysis, we found that high NLRs

were associated with poorer DFS. Furthermore, the results of the Cox regression analysis showed that NLR was not an independent prognostic factor for DFS in HCC patients. However, in the subgroup analysis, we found that NLR was an independent influential factor in predicting DFS in NBNC-HCC patients.

The mechanisms by which a high NLR is associated with poor prognosis are not fully understood. Inflammatory states promote tumour proliferation and provide an environment conducive to malignant tumour growth, and inflammation-related factors also stimulate malignant tumour angiogenesis, invasion and metastasis [26, 27]. As NLR represents the inflammatory state of the host, a high NLR may be associated with poor prognosis in cancer patients because a high NLR implies that there are elevated levels of neutrophils and reduced levels of lymphocytes, and these cell types are known to mediate antitumor responses and the release of cytokines, such as interleukin-1 and interleukin-6 by neutrophils, as well as tumour necrosis factors that promote tumour growth. High NLRs in patients, who have decreased lymphocyte counts, may be associated with decreased immune responses and increased neutrophil counts and may also be associated with tumour progression; therefore, a high NLR may be an important poor prognostic factor for cancer patients. We provide evidence that NLR is an independent predictor of prognosis in patients with NBNC-HCC after hepatectomy and that preoperative adjuvant therapy may be considered for patients with high preoperative NLR levels. This is of value in guiding aggressive individualized interventions and follow-up.

There are some limitations of this study, which are as follows. First, although the neutrophil and lymphocyte counts may be influenced by medications or other factors, we did not consider these factors, which may have had an impact on the results. Second, the sample size of this study was limited, and it was a retrospective study. The heterogeneity of the patients and treatments may have influenced the actual results. Prospective studies with large samples are still needed to confirm the effect of NLR on the survival of NBNC-HCC patients and the validity and sensitivity of this index.

Conclusion

A higher preoperative NLR in NBNC-HCC patients may indicate a later stage of surgery. A preoperative NLR of 2.63 was used to determine the cut-off value of the prognosis of patients with NBNC-HCC, and the prognosis of patients with a preoperative NLR>2.63 was worse than that of patients with an NLR≤2.63. The preoperative NLR is expected to be a prognostic marker for NBNC-HCC patients.

Abbreviations

HBV: Hepatitis B virus;

HCC: Hepatocellular carcinoma;

HCV: Hepatitis C virus;

NBNC- HCC: non-B non-C HCC;

NAFLD: Non-alcoholic fatty liver;

B-HCC: Hepatitis B virus related hepatocellular carcinoma;

DFS: Disease-free survival;

OS: Overall survival;

ALT: Alanine aminotransferase;

AST: Aspartate aminotransferase;

AFP: Alpha-Fetoprotein;

Declarations

Acknowledgements

None

Authors' contributions

XPT study design, data collection, data analysis and interpretation, draft of the manuscript, approval of final manuscript, supervision. PF, SWJ study design, data collection, data analysis and interpretation, draft of the manuscript, approval of final manuscript, supervision. WC study design, data analysis and interpretation, revision of the manuscript, approval of final manuscript. All authors approved the final version of the manuscript.

Funding

This study was supported by the Guangdong Natural Science Foundation (2014A030310021) National Natural Science Foundation Project, Regional Science Foundation Project (Grant Number: 81260368).

Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in compliance with all national and international ethical standards for research with humans. All study procedures were approved by the Ethics Committee of Jiangxi Provincial People's Hospital and patients gave written informed consent before being enrolled.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

[1] Department of Emergency, The Second Affiliated Hospital of Guangzhou medical university, Guangzhou, 510655, China.

[2] Department of General Surgery, Jiangxi Provincial People's Hospital Affifiliated to Nanchang University, Nanchang, 330006, Jiangxi, China.

[3] Department of Pharmacy, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China

[4] Department of Colorectal Surgery, The Six Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510655, China.

[5] Guangdong Provincial Key laboratory of Colorectal and Pelvic Floor Disease, The Sixth Affiliated Hospital of Sun Yat-sen University, 510655, Guangzhou, China.

[6] Guangdong Research Institute of Gastroenterology, The Sixth Affiliated Hospital of Sun Yat-sen University, 510655, Guangzhou, China.

References

1. Nie W, Yan L, Lee YH, et al. Advanced mass spectrometry-based multi-omics technologies for exploring the pathogenesis of hepatocellular carcinoma[J]. Mass Spectrometry Reviews, 2016, 35(3):331-349.
2. Chen W, Liang JL, Zhou K, et al. Effect of CIP2A and its mechanism of action in the malignant biological behavior of colorectal cancer[J]. Cell Communication and Signaling, 2020, 18(1):1-16.
3. Ransome E, Tong L, Espinosa J, et al. Trends in surgery and disparities in receipt of surgery for intrahepatic cholangiocarcinoma in the US: 2005-2014[J]. Journal of Gastrointestinal Oncology, 2019, 10(2):339-347.
4. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States[J]. New England Journal of Medicine, 1999, 340(10):745-750.
5. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: A weighty connection[J]. Hepatology, 2010, 51:1820-1832.

6. Masashi U, Koji K, Naoyuki T, et al. Preoperative Albumin-to-Globulin Ratio Predicts Prognosis in Hepatocellular Carcinoma: A Cohort Study Including Non-Hepatitis Virus-Infected Patients[J]. Digestive surgery, 2021, 38(4):307-315.
7. Xie JY, Wei JX, Lv LH, et al. Angiopoietin-2 induces angiogenesis via exosomes in human hepatocellular carcinoma[J]. Cell Communication and Signaling, 2020, 18(1):46.
8. Diao P, Wu Y, Jin L, et al. Preoperative systemic immune-inflammation index predicts prognosis of patients with oral squamous cell carcinoma after curative resection[J]. Journal of Translational Medicine, 2018, 16(1):365.
9. Kumano Y, Hasegawa Y, Kawahara T, et al. Pretreatment Neutrophil to Lymphocyte Ratio (NLR) Predicts Prognosis for Castration Resistant Prostate Cancer Patients Underwent Enzalutamide[J]. BioMed Research International, 2019, 2019:1-5.
10. Lalosevic MS, Markovic AP, Stankovic S, et al. Combined Diagnostic Efficacy of Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Mean Platelet Volume (MPV) as Biomarkers of Systemic Inflammation in the Diagnosis of Colorectal Cancer[J]. Disease Markers, 2019, 2019:1-7.
11. Mouchli M, Reddy S, Gerrard M, Boardman L, Rubio M. Usefulness of neutrophil-to-lymphocyte ratio(NLR) as a prognostic predictor after treatment of hepatocellular carcinoma. Annals of Hepatology, 2021, 22:100249.
12. Pirozzolo G, Gisbertz SS, Castoro C, et al. Neutrophil-to-lymphocyte ratio as prognostic marker in esophageal cancer: a systematic review and meta-analysis[J]. Journal of Thoracic Disease, 2019, 11(7):3136-3145.
13. Vartolomei MD, Porav-Hodade D, Ferro M, et al. Prognostic role of pretreatment neutrophil-to-lymphocyte ratio (NLR) in patients with non muscle-invasive bladder cancer (NMIBC): A systematic review and meta-analysis[J]. Urologic Oncology, 2018, 36(9):389-399.
14. Hayashi M, Yamada S, Takano N, et al. Different Characteristics of Serum Alfa Fetoprotein and Serum Des-gamma-carboxy Prothrombin in Resected Hepatocellular Carcinoma[J]. In vivo(Athens, Greece), 2021, 35(3):1749-1760.
15. Shinkawa H, Tanaka S, Takemura S, et al. Outcomes of Non-B Non-C Hepatocellular Carcinoma with Reference to Patients with Interferon-Induced Hepatitis C Virus Eradication[J]. Journal of Gastrointestinal Surgery, 2019, 24(8):1809-1817.
16. Nagaoki Y, Hyogo H, Aikata H, et al. Recent trend of clinical features in patients with hepatocellular carcinoma[J]. Hepatology Research, 2012, 42(4):368-375.
17. Ringelhan M, Pfister D, O'Connor T, et al. The immunology of hepatocellular carcinoma[J]. Nature Immunology, 2018, 19:222-232.
18. Chen W, Yi HJ, Chen XQ, et al. Prognostic value of the NLR combined with CIP2A in the serum of patients with colorectal cancer[J]. BMC Surgery, 2021, 21(1):297-304.
19. Miyamoto R, Inagawa S, Sano N, et al. The neutrophil-to-lymphocyte ratio (NLR) predicts short-term and long-term outcomes in gastric cancer patients[J]. European Journal of Surgical Oncology, 2018,

44(5):607-612.
20. Wang D, Bai N, Hu X, et al. Preoperative inflammatory markers of NLR and PLR as indicators of poor prognosis in resectable HCC[J]. PeerJ, 2019, 7(10):e7132.
21. Xue G, Zhang Y, Yang G. Predict value of peripheral blood NLR and PLR in non-luminal type of breast cancer with clinical progress disease in neoadjuvant chemotherapy[J]. Journal of Modern Medicine & Health, 2019, 35(17):2629-2632.
22. Okamura Y, Sugiura T, Ito T, et al. Neutrophil to lymphocyte ratio as an indicator of the malignant behaviour of hepatocellular carcinoma[J]. British Journal of Surgery, 2016, 103(7):891-898.
23. Lu SD, Wang YY, Peng NF, et al. Preoperative Ratio of Neutrophils to Lymphocytes Predicts Postresection Survival in Selected Patients with Early or Intermediate Stage Hepatocellular Carcinoma[J]. Medicine, 2016, 95(5):e2722.
24. Liu Y, Wang ZX, Cao Y, et al. Preoperative inflammation-based markers predict early and late recurrence of hepatocellular carcinoma after curative hepatectomy[J]. Hepatobiliary & Pancreatic Diseases International, 2016, 15(3): 266-274.
25. Hu XG, Mao W, Park YK, et al. Blood Neutrophil-to-Lymphocyte Ratio Predicts Tumor Recurrence in Patients with Hepatocellular Carcinoma within Milan Criteria after Hepatectomy[J]. Yonsei Medical Journal, 2016, 57(5):1115-1123.
26. Gomez D, Stiff GM, Toogood GJ, et al. Impact of systemic inflammation on outcome following resection for intrahepatic cholangiocarcinoma[J]. Journal of Surgical Oncology, 2008, 97(6):513-518.
27. Carlo ED, Forni G, Musiani P. Neutrophils in the antitumoral immune response[J]. Chemical Immunology & Allergy, 2003, 83:182-203.

Tables

Table 1

Comparison of clinicopathological features of NBNC-NLR(-)-HCC patients

Characteristic	NBNC-NLR(-)	B-NLR(+)	P	NBNC-NLR +	P	B-NLR(-)	P
Age (years)			0.004		<0.001		0.022
≥50	37	23		4		30	
<50	15	30		43		30	
Drink			<0.001		0.800		<0.001
Yes	42	15		37		22	
No	10	38		10		38	
BMI			<0.001		0.040		<0.001
25kg/m^2	26	4		14		12	
≤25kg/m^2	26	49		33		48	
Diabetes			0.006		0.095		0.396
Yes	11	2		6		9	
No	41	51		41		51	
Metabolic syndrome			<0.001		<0.001		<0.001
Yes	41	2		2		4	
No	11	51		45		56	
ALT			<0.001		0.451		<0.001
>40 U/L	10	36		12		38	
≤40 U/L	42	17		35		22	
AST			0.004		<0.001		0.033
>40 U/L	19	34		34		34	
≤40 U/L	33	19		13		26	
Tumor size (cm)			<0.001		<0.001		0.096
5	22	43		37		33	
≥5	30	10		10		27	
Secondary tumor			<0.001		<0.001		0.918

Yes	42	14		11	48	
No	10	39		36	12	
Portal violation			0.118		0.006	0.179
Yes	3	8		12	8	
No	49	45		35	52	
Pathological grade			0.103		0.154	0.001
I	8	3		3	0	
II-IV	44	50		44	60	
Postoperative treatment			0.199		0.373	0.170
No	29	36		22	41	
Yes	23	17		25	19	

Table 2

Univariate analysis of DFS and OS after HCC resection

Characteristic	DFS（P）	OS（P）
Age	0.983	0.259
NLR	0.009	0.056
BMI	<0.001	<0.001
Drink	0.002	0.179
Diabetes	0.159	0.825
Metabolic syndrome	0.947	0.062
ALT	0.195	0.528
AST	0.016	0.001
Tumor size	<0.001	<0.001
Secondary tumor	<0.001	<0.001
Portal violation	0.001	<0.001
Pathological grade	0.580	0.774

Table 3

Multivariate analysis of disease-free survival rate and overall survival rate after HCC resection

Characteristic	DFS			OS		
	95.0% CI for Exp(B)		P	95.0% CI for Exp(B)		P
	Lower	Upper		Lower	Upper	
NLR	0.647	1.525	0.975	-	-	-
BMI	0.972	1.008	0.264	0.976	0.996	0.005
AST	0.671	1.744	0.748	0.970	2.477	0.067
Tumor size	0.321	0.988	0.045	0.297	0.858	0.012
Secondary tumor	1.408	3.575	0.001	0.989	2.377	0.056
Portal violation	1.020	3.119	1.784	1.238	3.278	0.005
Drink	0.963	1.006	0.157	-	-	-

Table 4

Univariate analysis of postoperative DFS and OS in patients with NBNC-NLR(-)-HCC

Characteristic	DFS（P）	OS（P）
Age	0.082	0.062
NLR	0.002	0.486
BMI	< 0.001	< 0.001
Diabetes	0.339	0.657
Metabolic syndrome	0.875	0.356
ALT	0.946	0.730
AST	0.037	0.001
Tumor size	0.021	0.022
Secondary tumor	< 0.001	0.029
Portal violation	< 0.001	0.004
Pathological grade	0.600	0.985

Table 5

Multivariate analysis of disease-free survival rate and overall survival rate after NBNC-HCC resection

Characteristic	DFS			OS		
	95.0% CI for Exp(B)		P	95.0% CI for Exp(B)		P
	Lower	Upper		Lower	Upper	
NLR	1.233	7.080	0.015	-	-	-
AST	0.521	3.163	0.588	0.943	5.869	0.067
Tumor size	0.287	1.973	0.563	0.283	1.733	0.441
Secondary tumor	0.865	5.311	0.005	0.503	2.315	0.845
Portal violation	0.492	3.814	0.547	0.551	2.909	0.579
BMI	0.947	0.985	<0.001	0.924	0.973	<0.001

Table 6

The comparison between groups in terms of the DFS and OS

DFS(Month)	1	3	5	10
NBNC-NLR(-)	85.6	68.5	43.5	34.8
B-NLR(+)	33.1	30.3	27.3	16.4
NBNC-NLR(-)	85.6	68.5	43.5	34.8
NBNC-NLR(+)	42.3	32.2	-	-
NBNC-NLR(-)	85.6	68.5	43.5	34.8
B-NLR(-)	51.5	35.9	24.6	0.08
OS(Month)				
NBNC-NLR(-)	56.9	50.8	46.5	31.0
B-NLR(+)	58.9	41.4	36.0	29.1
NBNC-NLR(-)	56.9	50.8	46.5	31.0
NBNC-NLR(+)	64.5	40.1	30.6	-
NBNC-NLR(-)	56.9	50.8	46.5	31.0
B-NLR(-)	81.2	58.2	52.2	43.0

Figures

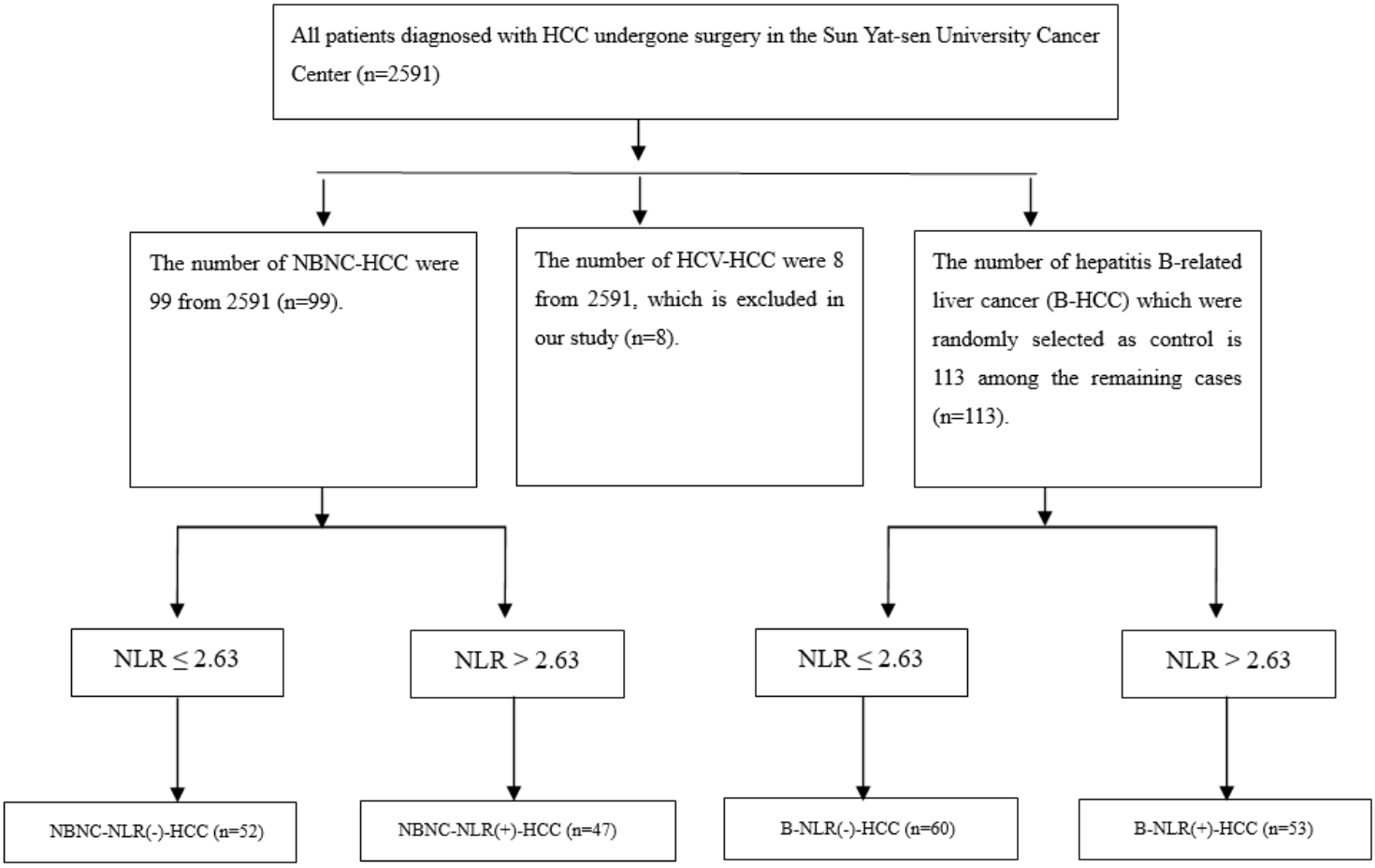

Figure 1

Flow chart of the screening process in this study. A total of 99 NBNC-HCC patients were selected from 2591 HCC patients who were treated at Sun Yat-sen University Cancer Center between January 1998 and December 2007.

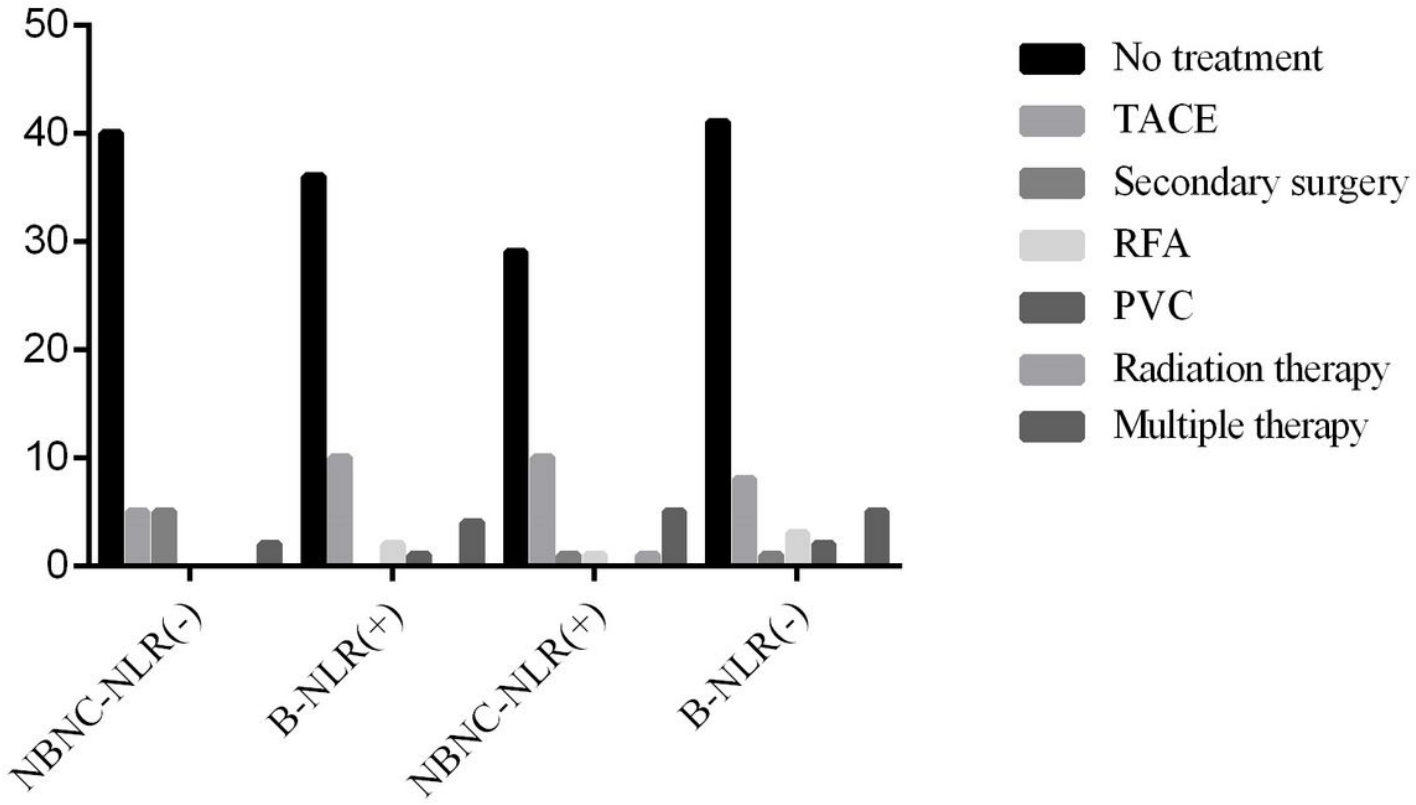

Figure 2

The number of HCC patients who underwent postoperative treatment in the NBNC-NLR (+)/(-)-HCC and B-NLR(+)/(-)-HCC groups.

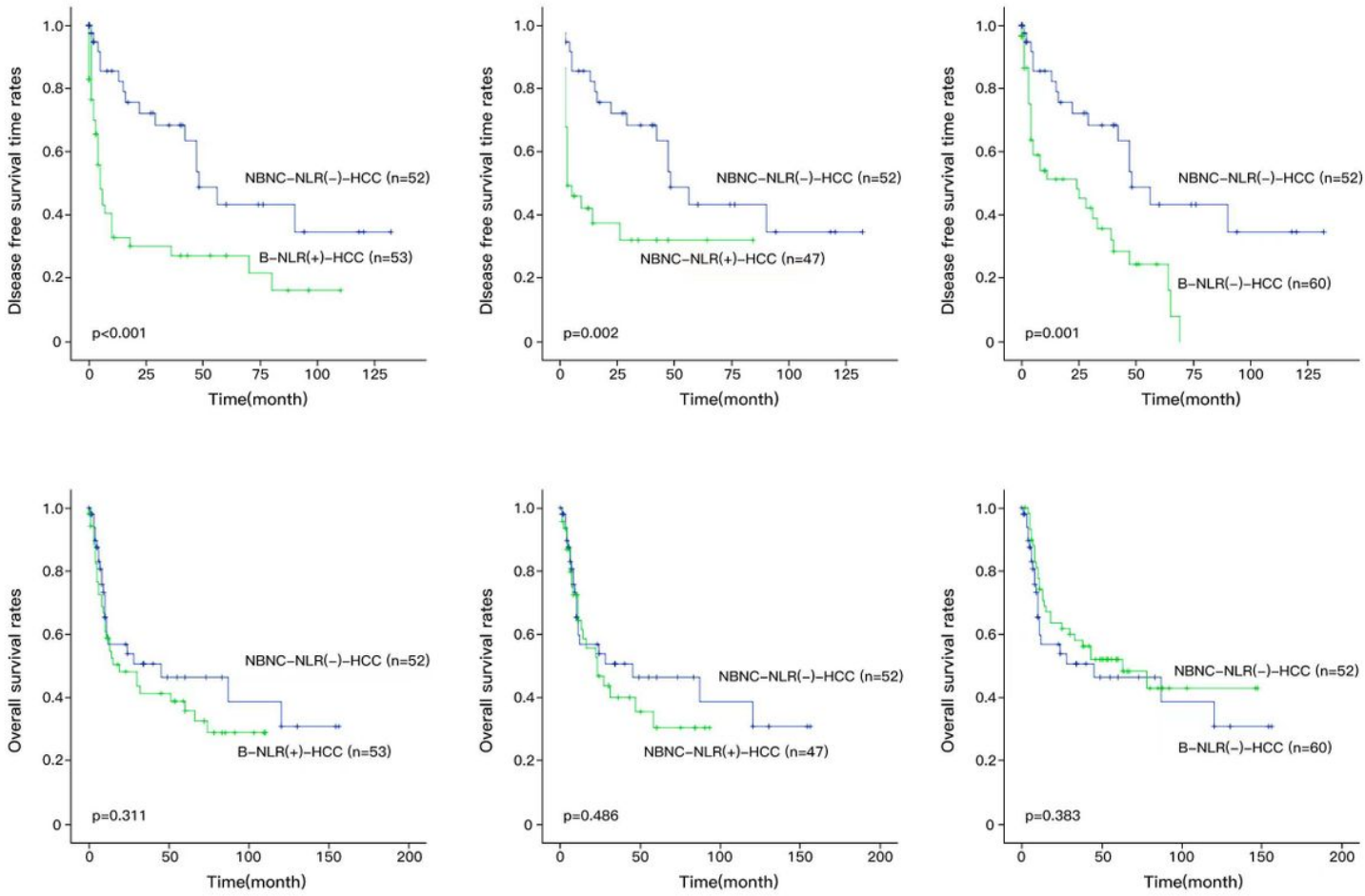

Figure 3

Comparison of the prognosis between the NBNC-NLR(-)-HCC patients and the other groups.