Inflammation-based Prognostic Score in Patients with Living Donor Liver Transplantation for Hepatocellular Carcinoma

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Abstract. *Background: Inflammation-based prognostic score including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), modified Glasgow prognostic score (mGPS) and prognostic nutritional index (PNI) have prognostic value in various malignancies. Patients and Methods: We retrospectively investigated their prognostic value in 213 patients with living donor liver transplantation (LDLT) for hepatocellular carcinoma (HCC). Disease-free survival (DFS) following LDLT was calculated; NLR, PLR, PNI and mGPS values in patients with and without recurrence were compared. Risk factors for HCC recurrence were identified by univariate and multivariate analyses. Results: Both NLR and PLR were significantly increased in patients with recurrence. Multivariate analysis showed that des-gamma-carboxy prothrombin (DCP) ≥ 300 mAU/ml, NLR ≥ 2.66 , < 3 months between last HCC treatment to LDLT were independent predictors of DFS. Conclusion: Preoperative NLR was an independent, inflammation-based prognostic marker of DFS and was predictive of recurrence following LDLT.*

Liver transplantation (LT) is currently the treatment of choice for early, unresectable hepatocellular carcinoma (HCC) in patients with poor liver function with candidate selection according to the Milan criteria (1 nodule of 5 cm or 2 to 3 nodules 3 cm in diameter) (1, 2). Some LT centers have broadened the indication to include the up to seven criteria (3) because of concerns that the Milan criteria are too stringent. In Japan, biomarkers, such as alfa-fetoprotein

(AFP), des-gamma-carboxy prothrombin (DCP) or neutrophil/lymphocyte ratio (NLR), in addition to tumor size and number, have been used to assess transplant candidates without decreasing long-term survival after living donor LT (LDLT) (4-6).

Preoperative nutritional and immunological statuses have been shown to be associated with not only postoperative complications but also long-term outcomes of patients with malignant tumors (7-9). In some patients, chronic inflammation was found to be an important prognostic factor even at an early stage of cancer progression (10-12). Inflammation markers, such as NLR, platelet/lymphocyte ratio (PLR), modified Glasgow prognostic score (mGPS) and prognostic nutritional index (PNI) have been evaluated for their prognostic value in patients with malignant tumors (13-17). A high NLR has been reported to predict poor survival in HCC patients after hepatic resection, radiofrequency ablation, transarterial chemoembolization (TACE) and LT. We recently found that NLR was an important prognostic factor in HCC patients after hepatic resection (18) and LDLT (19). Kinoshita *et al.* (20) reported that GPS was an independent marker of poor prognosis in patients with HCC and was superior to other inflammation-based prognostic variables. Yamamura *et al.* (21) reported that preoperative NLR was a better predictor of prognosis after hepatectomy than other inflammation markers. There have been few reports of the association of inflammation index scores and prognosis after LDLT for HCC, which was the primary objective of this study.

Patients and Methods

Patients' characteristics. A total of 213 LDLT for HCC were performed at the Kyushu University Hospital between October 1997 and December 2015. Following approval by the local Ethics and Indications Committee, the outcomes of 190 eligible patients who were observed for more than 6 months were analyzed retrospectively. Eleven patients who died within 3 months of transplantation were excluded from the analysis. The study selection

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Key Words: LDLT, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, prognostic nutritional index.

criteria included (i) LDLT as the only available curative modality for HCC and end-stage liver disease; (ii) no extrahepatic metastasis; and (iii) no significant vascular infiltration, such as by the portal vein or hepatic vein, indicating that there was no restriction on tumor size or number.

The transplant procedures for both the donors and recipients have been previously described (6). The immunosuppressive regimen consisted of a calcineurin inhibitor (tacrolimus or cyclosporin) plus a steroid with or without mycophenolate mofetil (MMF). Steroids (methylprednisolone 1 g) were given intravenously and the dose was tapered to 0 g by day 7. MMF (1 g/day) was started on postoperative day 1 and completed by 3 months. Maintenance immunosuppression therapy consisted of low-dose tacrolimus or cyclosporin from postoperative day 7.

Prognostic factors. The following variables were examined for their prognostic value with respect to HCC survival: sex (male *vs.* female); age (≥ 59 *vs.* < 59 years); hepatitis (HCV *vs.* non-HCV); Child-Pugh classification (A+B *vs.* C); Model for End-Stage Liver Disease (MELD) score (< 15 *vs.* ≥ 15); serum AFP (≥ 300 ng/ml *vs.* < 300 ng/ml); DCP (≥ 300 mAU/l *vs.* < 300 mAU/l); NLR (≥ 2.26 *vs.* < 2.26); PLR (≥ 70.44 *vs.* < 70.44); PNI (≥ 39.75 *vs.* < 39.75); number of tumors (≤ 3 *vs.* > 3); tumor size (≤ 5 cm *vs.* > 5 cm); interval between last HCC treatment and LDLT (< 3 months *vs.* ≥ 3 months); Milan criteria (yes *vs.* no); graft *versus* standard liver volume ($< 35\%$ *vs.* $\geq 35\%$); donor age (< 30 *vs.* > 30 years); graft (right/posterior *vs.* left); operation time (≤ 720 *vs.* > 720 min); and blood loss (≤ 10 l *vs.* > 10 l).

Patient follow-up. Clinical follow-up was carried out using a routine protocol that did not change during the study period. The patients were seen biweekly for the first month and then screened monthly for tumor markers, such as AFP and DCP for 6 months. Ultrasound (US) and enhanced computed tomography (CT) scans were done at 6-month intervals. When recurrence was suspected, additional testing, such as hepatic angiography was performed. The median duration of follow-up was 3.9 years.

Treatment of HCC recurrence. Patients with recurrences that could be surgically cured underwent tumor resection or ablation. Patients who were not candidates for surgical treatment were referred for palliative care by radiotherapy, TACE and systemic administration of fluorouracil (5-FU).

Histological evaluation. All the resected specimens were cut into serial 5- to 10-mm-thick slices and fixed in 10% formalin. After macroscopic examination, the largest slice was trimmed for embedding in paraffin, cut into 4- μ m serial sections and stained with hematoxylin-eosin. Tumor differentiation, microvascular invasion, intrahepatic metastasis and histological liver cirrhosis were evaluated by a pathologist according to criteria of the Liver Cancer Study Group of Japan (19).

Statistical analysis. Receiver operating characteristic (ROC) curves were generated and the area under the curve (AUC) was calculated to evaluate the discriminatory ability of each of the scoring systems and provide cut-off values to stratify the patient population. Continuous variables were expressed as means and standard deviations (SDs) and compared with Student's *t*-test. DFS was analyzed by the Kaplan-Meier method and compared with the log-

rank test. Variables that proved to be significant by univariate analysis were tested in a multivariate Cox proportional-hazard model. All analyses were performed with Statview 5.0 software (Abacus Concepts Inc., Berkeley, CA, USA). *p*-Values < 0.05 were considered statistically significant.

Results

The median follow-up was 64 months (range=6-162). HCC recurred in 28 patients (14.7%) with DFS rates 1, 3 and 5 years after LDLT of 92.7, 85.9 and 85.1%, respectively. Table I shows the AUC for recurrence with significant associations of inflammation cut-off scores of 2.66 for NLR (AUC=0.647, sensitivity 64.29%; specificity 66.07%) and 70.44 for PLR (AUC=0.704, sensitivity 85.71%; specificity 53.85%). C-reactive protein (CRP) and platelet count were also significant predictors of recurrence.

Univariate analysis showed that AFP ≥ 300 ng/ml, DCP ≥ 300 mAU/ml, NLR ≥ 2.66 , PLR ≥ 70.44 , platelet count $\geq 4.5 \times 10^4/\mu$ l, CRP > 0.27 mg/dl, tumor number ≥ 5 , tumor size ≥ 5 cm, interval between last HCC treatment and LDLT < 3 months, bilobar distribution, as well as exceeding the Milan criteria were associated with poor DFS (Table II). Following multivariate analysis, DCP ≥ 300 mAU/ml, NLR ≥ 2.66 , interval of < 3 months between the last HCC treatment and LDLT remained independent predictors of DFS (Table III). The 3-year DFS was 74.4% in patients with NLR ≥ 2.66 and 92.8% in patients with NLR < 2.66 (Figure 1A). The 3-year DFS was 76.0% in patients with PLR ≥ 70.44 and 95.2% in patients with PLR < 70.44 (Figure 1B). DCP ≥ 300 mAU/ml, NLR ≥ 2.66 , interval of < 3 months between last HCC treatment and LDLT remained independent predictors of DFS after multivariate analysis. Preoperative NLR was an inflammation-based independent predictor of DFS.

Discussion

We compared the prognostic value of inflammation-based indexes NLR, PLR, PNI and mGPS in a retrospective analysis of patients with LDLT for HCC. Multivariate analysis indicated that DCP ≥ 300 mAU/ml, NLR ≥ 2.66 and an interval between the last treatment to LDLT < 3 months were independent predictors of DFS. Preoperative NLR was the most useful of these inflammation markers as a predictor of recurrence.

We recently proposed new selection criteria for LDLT in patients with HCC (5). In this patient series, multivariate analysis identified tumor size, the presence of 8 or more tumors and an NLR of 4 or more as independent risk factors for post-LDLT tumor recurrence. These criteria could effectively exclude patients with biologically aggressive tumors before LT, thus promoting an extremely low recurrence rate. The reported rate of HCC recurrence after transplantation ranges from 8% to 22.7% (22-26) Patients

Table I. Area under the receiver operating characteristic (ROC) curve (AUC) and cut-off values for prognosis of recurrence by inflammation index score.

Value	Cut-off	AUC	Sensitivity	Specificity	p-Value
NLR	2.66	0.64732	0.6429	0.6607	0.0049
PLR	70.44	0.70435	0.8571	0.5385	0.0076
Platelets	4.5	0.65110	0.9286	0.3609	0.0197
CRP	0.27	0.66188	0.8214	0.5125	0.0431
PNI	39.75	0.53413	0.25	0.8935	0.7553
mGPS	0	0.53593	0.1429	0.9290	0.2068
Albumin	3.1	0.54522	0.5	0.6254	0.3892
WBC	3480	0.60704	0.6071	0.6095	0.3679
Neutrophils	1750	0.64751	0.7857	0.5207	0.1606
Lymphocytes	661	0.53487	0.3929	0.7160	0.3569

mGPS, Modified Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutritional index; CRP, C-reactive protein; WBC, white blood cells.

who experience recurrence after LT have rapid progression of disease and very poor prognosis with a median survival of from 7 to 9 months. The progression of recurrent HCC is more rapid after transplantation than after hepatic resection (25-28). The main reason for this poor outcome and rapid progression of disease is the immunosuppressed state maintained after transplantation. Hence, identification of selection criteria that avoid a decrease of long-term survival after LDLT is important.

There is evidence of a correlation of increased systemic inflammation with poor disease-specific survival in a number of different cancers. Both CRP level and NLR can detect the presence of a systemic inflammatory response. A high serum CRP level has been associated with portal vein invasion of cancer cells, while some reports have found an association of high preoperative serum CRP levels with early recurrence of HCC and poor survival after hepatic resection (29). The PLR, which is calculated from the platelet and total lymphocyte counts in the peripheral blood, is a less well-studied inflammatory marker but was reported by Lai *et al.* (30) to predict post-LT tumor recurrence. The mGPS, which combines serum CRP and albumin levels, is widely accepted as a marker of chronic inflammation in patients with cancer, including HCC (13, 20). CRP and albumin are produced in the liver and liver function may reflect the levels of both proteins. PNI, which is calculated from the serum albumin concentration and total lymphocyte count in the peripheral blood, was first used to assess perioperative immunonutritional status and surgical risk in patients undergoing gastrointestinal surgery (5). The PNI has recently been shown to be a prognostic marker in various malignancies, including HCC (14, 31, 32).

Figure 1. Kaplan-Meier cumulative survival analysis of HCC patients with LDLT. DFS in patients with $\text{NLR} \geq 2.66$ was significantly worse than in those with $\text{NLR} < 2.66$ (A). DFS rate in patients with $\text{PLR} \geq 70.44$ was significantly worse than in those with $\text{PLR} < 70.44$ (B). HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; DFS, disease-free survival; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

Three reports have compared the prognostic value of inflammation-based prognostic scores for predicting tumor recurrence after curative resection for HCC (20, 21, 33). Kinoshita *et al.* (20) and Huang *et al.* (33) reported that mGPS was superior, whereas Yamamura *et al.* (21) reported NLR was superior to other markers of inflammation. Parisi *et al.* (34) failed to demonstrate a significant association between NLR, PLR and HCC inflammation scores and post-LT recurrence in patients within the Milan criteria. Lai *et al.* (30) found that PLR was a good predictor of risk of post-LT recurrence. There are no previous reports of the relationship between inflammation-based scores and HCC recurrence after LDLT.

The molecular mechanism associated with elevated NLR and HCC prognosis involves many factors, although poorly understood. Chronic systemic inflammation is an important prognostic factor in cancer patients and the NLR has been

Table II. Univariate analysis of clinicopathological characteristics and recurrence of HCC.

Characteristic	Patients (n)	3-year survival (%)	p-Value	Characteristic	Patients (n)	3-year survival (%)	p-Value
Gender				Stage			
Male	107	85.2	0.868	I+II	114	93.1	0.001
Female	83	86.2		III+IV	76	75.3	
Age (year)				Tumor location:			
<59	93	85.0	0.962	unilobular	106	91.8	0.003
≥59	97	85.9		bilobular	84	78.3	
Hepatitis				Number of tumors			
HCV	134	84.6	0.459	≤3	149	91.6	0.613
Non-HCV	56	88.1		>3	41	63.9	
Child-Pugh classification				Tumor size (cm)			
A+B	76	84.8	0.579	≤5	182	88.3	0.001
C	114	86.0		>5	8	25.0	
MELD score				Duration of last treatment to LDLT			
<15	130	86.0	0.939	<3 months	25	70.6	0.001
≥15	60	84.4		≥3 months	165	87.7	
AFP (ng/ml)				Milan criteria			
<300	160	91.0	0.001	Yes	124	93.4	0.001
≥300	30	58.0		No	66	70.9	
DCP (mAU/ml)				GV/SLV (%)			
<300	159	92.0	0.001	<35	41	86.7	0.622
≥300	31	52.9		≥35	149	84.9	
NLR				Age of donor (years)			
<2.66	118	92.3	0.001	≤30	73	84.0	0.213
≥2.66	72	74.4		>30	117	86.5	
PLR				Graft			
<70.44	93	95.2	0.001	Right/posterior	78	90.5	0.187
≥70.44	97	76.0		Left	112	82.0	
PNI				Operation time (min)			
<39.75	166	98.6	0.182	≤720	73	89.6	0.187
≥39.75	24	77.2		>720	117	82.8	
mGPS				Blood loss (l)			
0	16	79.1	0.185	≤10	169	85.0	0.174
1	174	86.1		>10	18	93.8	
CRP (ng/ml)							
<0.27	92	92.0	0.001				
≥0.27	98	77.7					
Platelet (/μl)							
≤45000	65	80.5	0.006				
>45000	125	95.3					

HCC, Hepatocellular carcinoma; LDLT, living donor liver transplantation; HCV, hepatitis C virus; MELD, Model for End-Sage Liver Disease; AFP, alpha-fetoprotein; DCP, des-gamma carboxy prothrombin; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutrition index; mGPS, modified Glasgow prognostic score; CRP, C-reactive protein; GV/SLV: graft *versus* standard liver volume.

used as an indicator of chronic inflammation. We previously showed that NLR was an important prognostic marker in HCC patients after hepatic resection (18) and after LDLT (19). A close relationship between accumulation of tumor-associated macrophages (TAMs) and high NLR values was observed in HCC patients with hepatic resection and LDLT (35). A high NLR is associated with a high infiltration of TAMs and high production of inflammatory cytokines, such as interleukin (IL)-6 and IL-8 that promote systemic neutrophilia. TAMs have also been reported both as a major component of the tumor inflammatory microenvironment

and as promoters of cell proliferation and tumor angiogenesis. Monocytes are recruited from the circulation into sites containing healthy or malignant tissue and then differentiate into macrophages. TAMs produce cytokines and a high NLR might reflect the accumulation of TAMs, as well as local cytokine production.

In conclusion, preoperative NLR in HCC patients with LDLT was the most useful predictor of recurrence among the inflammation-based prognostic indicators. A multicenter study is required to provide additional evidence of the significance of NLR in HCC.

Table III. Multivariate analysis and Cox proportional-hazard model of clinical characteristics and recurrence-free survival in HCC patients with LDLT.

Variables	Odds ratio	Hazard ratio	p-Value
DCP ≥ 300 (mAU/l)	4.239	1.644-10.931	0.003
Multiple tumor number (≥ 5)	4.340	1.424-13.225	0.011
NLR ≥ 2.66	2.770	1.089-7.042	0.032
PLR ≥ 70.44	3.226	0.921-11.364	0.067
CRP ≥ 0.27 (mg/dl)	3.030	0.896-10.301	0.074
Duration of last treatment to LDLT			
<3 months	2.398	0.878-6.550	0.088
Tumor location: bilobular	2.699	0.682-10.691	0.157
Tumor size (>5 cm)	1.938	0.545-6.899	0.307
AFP ≥ 300 (ng/ml)	1.615	0.613-4.255	0.308
Above Milan criteria	1.692	0.144-2.415	0.464
Stage (III+IV)	1.538	0.417-5.650	0.518
Platelets $\leq 45,000/\mu\text{l}$	1.356	0.356-5.168	0.660

HCC, Hepatocellular carcinoma; LDLT, living donor liver transplantation; AFP, alpha-fetoprotein; DCP, des-gamma carboxy prothrombin; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutrition index; CRP, C-reactive protein.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Financial Support

The study did not receive grants or any other financial support.

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Received August 26, 2016

Revised September 7, 2016

Accepted September 8, 2016