Original article

Nuclear Medicine Communications

Analysis of prognostic factors in patients receiving transarterial radioembolization for unresectable hepatocellular carcinoma

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Aim **This study aimed to analyze the prognostic factors of patients receiving transarterial radioembolization for unresectable hepatocellular carcinoma.**

Material and method **Eighty-six (73 M and 13F; mean age: 64.3 ± 9.8 years) patients who received transarterial radioembolization for unresectable hepatocellular carcinoma were included. Relationship between serum alpha-fetoprotein and international normalization ratio level, albumin-bilirubin grade, neutrophil-lymphocyte ratio, presence of portal venous thrombosis and extrahepatic metastases, the dimension of index lesion and OS were analyzed.**

Results **Neutrophil lymphocyte ratio was ≤ 5 in 76 (88%) and >5 in 10 (12%) of patients. Sixty-two (72%) patients died during a mean of 25.6± 9.7 months follow-up. Mean OS for all patients was calculated as 12.9 ± 14.6 months. In univariate analysis, albumin-bilirubin grade (22.3 ± 3.8 vs. 11.6 ± 4.2; *P* = 0.03), neutrophil-lymphocyte ratio (21.8 ± 3.6 vs. 7.3 ± 2.6; *P* =0.04), presence of extrahepatic metastases (30.1 ± 5.4 vs. 7.4 ± 2.0; *P* = 0.001) and portal venous thrombosis (26.5± 4.8 vs. 10.5 ± 2.1; *P* = 0.01) had significant effect on OS. In multivariate analysis, serum international normalization ratio (*P* = 0.005) and alpha-fetoprotein level (*P* = 0.004), albumin-bilirubin grade (*P* = 0.05), neutrophil-lymphocyte ratio (*P* = 0.007), Child-Pugh score (0.006) and presence of ascites (*P* = 0.005) were significantly correlated with OS.**

Conclusion **Patients with low basal albumin-bilirubin grade and neutrophil-lymphocyte ratio survive longer after transarterial radioembolization for unresectable hepatocellular carcinoma. Presence of extrahepatic metastases and portal venous thrombosis seems to have a prognostic value.** ***Nucl Med Commun*** **41:73–77**
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Nuclear Medicine Communications 2020, **41**:73–77

Keywords: hepatocellular carcinoma, prognostic factors, radioembolization

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Received 26 September 2019 **Accepted** 31 October 2019

Introduction

The liver is a frequent organ of primary and secondary tumors, and hepatocellular carcinoma (HCC) is the most common primary liver tumor [1]. Surgical resection and transplantation is the first choice of treatments for early-stage HCCs [2]. However, surgical procedures are not feasible in most of the patients due to location and dissemination of the primary tumor [3].

Therefore, the majority of patients with unresectable HCC are referred for local ablative treatments such as transarterial chemo-embolization (TACE) and transarterial radioembolization (TARE). Both of these treatments based on the preferentially arterial blood supply of liver tumors, that allows specific targeting of tumor with sparing of the healthy liver tissue [4]. TARE with Yttrium-90 (Y-90) resin or glass microspheres has been proved to be a safe and effective treatment for locally advanced HCC [5,6].

Unlike metastatic tumors, in HCC patients, the liver reserve is the primary concern during pretreatment evaluation of patients referred for TARE. Different clinical and laboratory parameters are considered to assess the liver reserve. Thus, all the patients who underwent TARE for HCC fit the strict criteria, prognosis and survival differs among the patients. For this reason, new parameters or scoring systems have been researched to predict which group of patients would have better prognosis after TARE [7–10].

In this single-center study, we aimed to analyze the prognostic effects of different baseline descriptive, laboratory and radiological parameters in patients who receive TARE for unresectable HCC.

Materials and methods

Patients

The study was designed as retrospective documentation of the data of 86 (73 M and 13 F; mean age: 64.3 ± 9.8) patients receiving TARE for unresectable HCC. Baseline and follow-up data of patients were obtained from the hospital database. To analyze the possible effect on

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DOI: 10.1097/MNM.0000000000001122

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survival; age, sex, serum alpha-fetoprotein (AFP), international normalization ratio (INR), albumin, bilirubin levels, total blood count parameters, presence of portal venous thrombosis (PVT), extrahepatic metastases, the dimension of index lesion were noted. Albumin-bilirubin (ALBI) grade and neutrophil-lymphocyte ratio (NLR) were calculated.

Radioembolization

Resin and glass microspheres were used in 80 (93%) and six (7%) of the patients. Each pretreatment workup included computed tomography or MRI, up-to-date blood laboratory test results, and clinical examination. The widely accepted parameters of liver reserve, bone marrow reserve (granulocytes >1500/μl, platelets >60 000/μl), and hepatic vascularity were used as inclusion and exclusion criteria for TARE. The liver reserve was assessed with serum bilirubin, aspartate transaminase, alanine transaminase, and alkaline phosphatase levels. For radioembolization, bilirubin level below 2 mg/dl and AST, ALT and ALP levels less than five times the standard upper limit required.

Additionally, Child-Pugh (CP) score and presence of ascites and encephalopathy were studied to evaluate liver reserve. A therapy-planning angiography was performed to evaluate the vascular tree. All patients were hospitalized overnight, and medications such as analgesics, antiemetics, and H2 antagonists were administered, as needed. All patients were monitored closely until acute or late toxicities were resolved, and long-term follow-up data were noted for disease recurrence and death.

Data and statistical analysis

Continuous parameters were described as mean values and ±SD, and categorical data were described as number (n) and percentage (%). For the comparison of OS of the groups, Kaplan–Meier analysis and life tables were used. Multivariate analysis of the effect of different parameters on OS was analyzed with Cox regression analysis. A P value less than 0.05 was considered statistically significant. Relationship between serum AFP and INR level, ALBI grade, NLR, presence of PVT, extrahepatic metastases, the dimension of index lesion and OS were analyzed.

Results

Patients

HCC was developed on the underlying cirrhotic disease in 66 (77%) patients. Although 13 (15%) of patients had a history of liver surgery, 13 (15) and 12 (14%) had a failure of previous radiofrequency ablation and TACE. CP grade was calculated as A, B and C in 54 (63%), 24 (28%) and three (3%) of patients, respectively. Although seven (8%) patients were in Barcelona clinic liver cancer (BCLC) stage A group, 54 (63%) and 25 (29%) patients were in B and C groups, respectively. Mean ± SD of the index lesion size was calculated as 65.1 ± 44.6 mm. Pretreatment assessment revealed extrahepatic metastases in 20 (23%) patients and PVT in 30 (35%) patients. Median serum AFP level was 24.4 ng/ml (min-max: 1.4-49289). ALBI grade was one and two in 67 (78%) and 19 (22%) of patients. NLR was ≤5 in 76 (88%) and >5 in 10 (12%) of patients. Baseline data of the patient group is given in Table 1.

Survival analysis

Sixty-two (72%) patients died during mean 25.6 ± 9.7 months follow-up. Mean OS for all patients was calculated as 12.9 ± 14.6 months. In univariate analysis, ALBI grade (22.3 ± 3.8 vs. 11.6 ± 4.2; P = 0.03), NLR (21.8 ± 3.6 vs. 7.3 ± 2.6; P = 0.04), presence of extrahepatic metastases (30.1 ± 5.4 vs. 7.4 ± 2.0; P = 0.001) and PVT (26.5 ± 4.8 vs. 10.5 ± 2.1; P = 0.01) had significant effect on OS (Table 2 and Fig. 1). In multivariate analysis, serum INR (P = 0.005) and AFP levels (P = 0.004), ALBI grade (P = 0.05), NLR (P = 0.007), CP score (P = 0.006) and the presence of ascites (P = 0.005) were significantly correlated with OS (Table 3).

Discussion

TARE candidates generally are patients who have intermediate or advanced stage HCC, and they are not suitable for TACE. In this patient population, survival is mostly correlated with liver reserve. CP is one of the most known scoring systems to assess liver function and based on the evaluation of serum bilirubin and albumin levels,

Table 1 Baseline data of the patient group

Parameter	n(%)
Underlying cirrhosis	
Yes	66 (77)
No	20 (23)
Previous treatments	
Surgery	13 (15)
RFA	13 (15)
TACE	12 (14)
Child-Pugh score	
A	54 (63)
B	24 (28)
C	3 (3)
BCLC stage	
A	7 (8)
B	54 (63)
C	25 (29)
Presence of extrahepatic metastases	
Yes	20 (23)
No	66 (77)
Presence of PVT	
Yes	30(35)
No	56 (65)
ALBI grade	
1	67 (78)
2	19 (22)
NLR	
≤5	76 (88)
>5	10 (12)

ALBI, albumin-bilirubin grade; BCLC, Barcelona clinic liver cancer; NLR, neutrophil-lymphocyte ratio; PVT, portal venous thrombosis; RFA, radiofrequency ablation; TACE, transarterial chemotherapy.

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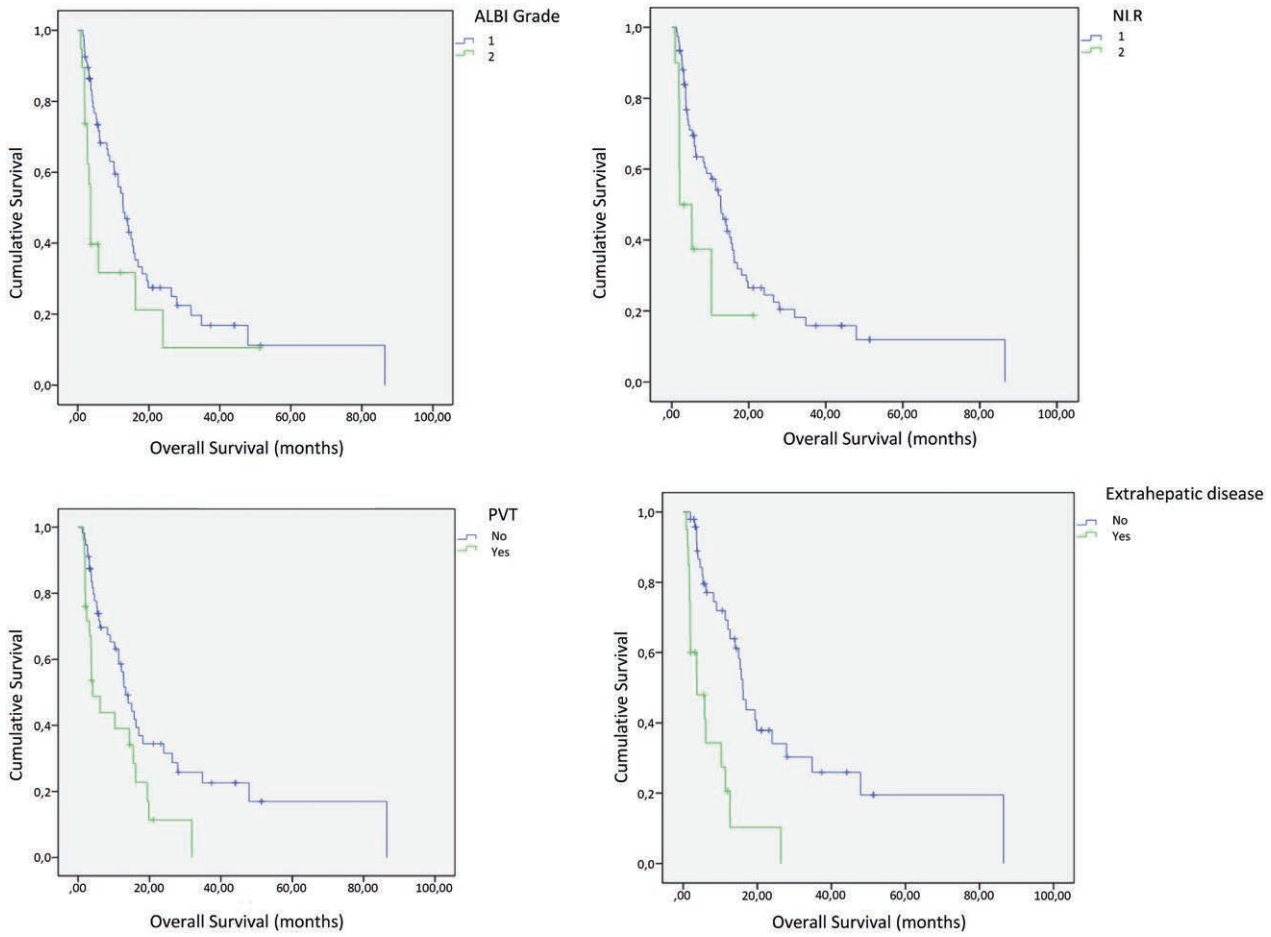
Table 2 Summary of univariate analysis of the effects of different parameters on OS

Parameter	Mean	SD	*P* value
Sex			
M	13.5	3.2	0.89
F	21.4	3.7	
ALBI grade			
1	22.3	3.8	0.03
2	11.6	4.2	
NLR			
≤5	21.8	3.6	0.04
>5	7.3	2.6	
Child-Pugh score			
A	23.9	7.2	0.43
B	12.3	5.2	
C	5.8	0.1	
BCLC stage			
A	7.9	2.6	0.47
B	22.8	8.1	
C	19.8	7.5	
Presence of extrahepatic metastases			
Yes	7.4	2	0.001
No	30.1	5.4	
Presence of PVT			
Yes	10.5	2.1	0.01
No	26.5	4.8	

ALBI, albumin-bilirubin grade; BCLC, Barcelona clinic liver cancer; NLR, neutrophil-lymphocyte ratio; PVT, portal venous thrombosis.

presence of ascites, neurological disorder and nutritional status [11]. CP classification system divides patients into three groups and is initially identify suitable patients for portal decompression. In 1973, CP scoring system was revised but its purpose remained unchanged. Johnson *et al.* [12] developed a newer model, known as ALBI grading system, from a large Japanese population with HCC, to assess liver function and their data were confirmed in different patient populations. Recently, the effect of ALBI grades on patients who received TARE for unresectable HCC was investigated in two large series. Gui et al. found that patients with ALBI grade 1 had superior survival than those with ALBI grade 2. Though, they have not found a significant difference in the survivals of CP class A and class B patients [8]. In our series, we have not found a significant difference of OS among groups with different CP score in univariate analysis. However, CP score is a significant parameter in multivariate analysis. Mohammadi *et al.* evaluated ALBI grade as a prognostic factor in 124 patients. They concluded that ALBI is more sensitive than CP in the setting of mild dysfunction [13].

Fig. 1



Kaplan–Meier survival curves among groups based on different prognostic factors.

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Table 3 Summary of multivariate analysis

Parameter	*P* value
INR	0.005
NLR	0.007
Presence of PVT	0.12
BCLC stage	0.56
ALBI Grade	0.05
Presence of extrahepatic metastases	0.85
Serum AFP level	0.004
Child-Pugh score	0.006
Presence of ascites	0.005

AFP, alpha fetoprotein; ALBI, albumin-bilirubin grade; BCLC, Barcelona clinic liver cancer; INR, international normalization ratio; NLR, neutrophil lymphocyte ratio; PVT, portal venous thrombosis.

Tumor load is another important parameter to determine of survival of HCC patients. BCLC staging system is widely used to describe intrahepatic tumor load in combination with liver reserve. In this study, the majority of the patients were BCLC stage B and mean OS was calculated as 12.9 months. Hilgard *et al.* [14] reported a median OS of 16.8 months in their study, in which 208 patients were included. In another study, Sangro *et al.* [15] calculated a 16.9 months OS for their group. Both studies were performed mostly on BCLC B patients. Our shorter OS times might be related to the relatively higher incidence of PVT. In a recent meta-analysis, Rognoni *et al.* [16] suggested that OS halved to 6–12 months from 12 to 24 months in patients who received TARE for intermediate-advanced stage HCC in the presence of PVT. In support of this suggestion, in our analysis, median OS of patients with PVT found significantly shorter than those without. Similarly, OS of patients with PVT have been reported significantly shorter in previous studies [17,18].

Ideally, TARE is performed in liver limited HCCs; however, it has also been applied in the presence of limited extrahepatic disease. In our series, 35% of patients had an extrahepatic disease, and we found that patients with extrahepatic disease had shorter OS compared to those without in univariate analysis. This difference was NS in multivariate analysis. Ali *et al.* have demonstrated that the presence of metastatic disease is a poor prognostic factor. In their series, consisting of 547 patients, uni- and multi-variate analysis showed more prolonged survival in patients with liver limited disease [18]. The lack of significance in our multivariate analysis can be attributed to the limited number of patients. Additionally, in our multivariate analysis, pretreatment serum AFP level has been found to be a significant factor to predict survival. This result is expected since AFP has been used as a diagnostic, screening and prognostic tool for HCC [19–21].

NLR was a significant factor in uni- and multi-variate analysis of our study. Patients with higher basal NLR levels–higher than 5–found to survive shorter than those with lower NLR level. Due to the tumorigenic role of systemic inflammation and upregulation of cytokines, studies have suggested the value of blood NLR as an indicator of future survival in patients with resectable and unresectable HCC [22–24]. Although the prognostic robustness of NLR stands in the context of liver transplantation, hepatectomy, transarterial chemoembolization, and sorafenib interventions, the use of this tool in the setting of RE has been assessed in a limited number of studies [25–30]. Howbeit different cutoff values were selected for NLR, 5 was chosen and evaluated as the cut-off value in this study.

The retrospective design and limited number of included patients are the major limitations of our study. However, unlike previous studies, different prognostic factors were assessed together.

Conclusion

Patients with low basal ALBI grade and NLR survive longer than those with higher levels after TARE for unresectable HCC. Presence of PVT and extrahepatic metastases seems to have a prognostic significance; however confirmation is needed with larger patient groups.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Wallace MC, Preen D, Jeffrey GP, Adams LA. The evolving epidemiology of hepatocellular carcinoma: a global perspective. *Expert Rev Gastroenterol Hepatol* 2015; **9**:765–779.

2 Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**:1020–1022.

3 El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**:1118–1127.

4 Duran R, Chapiro J, Schernthaner RE, Geschwind JF. Systematic review of catheter-based intra-arterial therapies in hepatocellular carcinoma: state of the art and future directions. *Br J Radiol* 2015; **88**:20140564.

5 Goin JE, Salem R, Carr BI, Dancey JE, Soulen MC, Geschwind JF, *et al.* Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: a risk-stratification analysis. *J Vasc Interv Radiol* 2005; **16**:195–203.

6 Braat MN, Samim M, van den Bosch MA, Lam MG. The role of 90Y-radioembolization in downstaging primary and secondary hepatic malignancies: a systematic review. *Clin Transl Imaging* 2016; **4**:283–295.

7 Jreige M, Mitsakis P, Van Der Gucht A, Pomoni A, Silva-Monteiro M, Gnesin S, *et al.* 18F-FDG PET/CT predicts survival after 90Y transarterial radioembolization in unresectable hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging* 2017; **44**:1215–1222.

8 Gui B, Weiner AA, Nosher J, Lu SE, Foltz GM, Hasan O, *et al.* Assessment of the albumin-bilirubin (ALBI) grade as a prognostic indicator for hepatocellular carcinoma patients treated with radioembolization. *Am J Clin Oncol* 2018; **41**:861–866.

9 Blanc-Durand P, Van Der Gucht A, Jreige M, Nicod-Lalonde M, Silva-Monteiro M, Prior JO, *et al.* Signature of survival: a 18F-FDG PET based whole-liver radiomic analysis predicts survival after 90Y-TARE for hepatocellular carcinoma. *Oncotarget* 2018; **9**:4549–4558.

10 Spreafico C, Sposito C, Vaiani M, Cascella T, Bhoori S, Morosi C, *et al.* Development of a prognostic score to predict response to yttrium-90 radioembolization for hepatocellular carcinoma with portal vein invasion. *J Hepatol* 2018; **68**:724–732.

11 Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964; **1**:1–85.

12 Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, *et al.* Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol* 2015; **33**:550–558.

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13 Mohammadi H, Abuodeh Y, Jin W, Frakes J, Friedman M, Biebel B, *et al*. Using the albumin-bilirubin (ALBI) grade as a prognostic marker for radioembolization of hepatocellular carcinoma. *J Gastrointest Oncol* 2018; **9**:840–846.
14 Hilgard P, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, *et al*. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology* 2010; **52**:1741–1749.
15 Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, *et al*.; European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY). Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54**: 868–878.
16 Rognoni C, Ciani O, Sommariva S, Facciorusso A, Tarricone R, Bhoori S, Mazzaferro V. Trans-arterial radioembolization in intermediate-advanced hepatocellular carcinoma: systematic review and meta-analyses. *Oncotarget* 2016; **7**:72343–72355.
17 Floridi C, Pesapane F, Angileri SA, De Palma D, Fontana F, Caspani F, *et al*. Yttrium-90 radioembolization treatment for unresectable hepatocellular carcinoma: a single-centre prognostic factors analysis. *Med Oncol* 2017; **34**:174.
18 Ali R, Gabr A, Abouchaleh N, Al Asadi A, Mora RA, Kulik L, *et al*. Survival analysis of advanced HCC treated with radioembolization: comparing impact of clinical performance status versus vascular invasion/metastases. *Cardiovasc Intervent Radiol* 2018; **41**:260–269.
19 Trevisani F, De Notariis S, Rossi C, Bernardi M. Randomized control trials on chemoembolization for hepatocellular carcinoma: is there room for new studies? *J Clin Gastroenterol* 2001; **32**:383–389.
20 Nomura F, Ohnishi K, Tanabe Y. Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels. Analysis of 606 patients. *Cancer* 1989; **64**:1700–1707.
21 Lok AS, Lai CL. Alpha-fetoprotein monitoring in Chinese patients with chronic hepatitis B virus infection: role in the early detection of hepatocellular carcinoma. *Hepatology* 1989; **9**:110–115.
22 Huang ZL, Luo J, Chen MS, Li JQ, Shi M. Blood neutrophil-to-lymphocyte ratio predicts survival in patients with unresectable hepatocellular carcinoma undergoing transarterial chemoembolization. *J Vasc Interv Radiol* 2011; **22**:702–709.
23 Wei K, Wang M, Zhang W, Mu H, Song TQ. Neutrophil-lymphocyte ratio as a predictor of outcomes for patients with hepatocellular carcinoma undergoing TAE combined with sorafenib. *Med Oncol* 2014; **31**:969.
24 Gomez D, Farid S, Malik HZ, Young AL, Toogood GJ, Lodge JP, Prasad KR. Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. *World J Surg* 2008; **32**:1757–1762.
25 Motomura T, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, *et al*. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. *J Hepatol* 2013; **58**:58–64.
26 Xiao GQ, Liu C, Liu DL, Yang JY, Yan LN. Neutrophil-lymphocyte ratio predicts the prognosis of patients with hepatocellular carcinoma after liver transplantation. *World J Gastroenterol* 2013; **19**:8398–8407.
27 Mano Y, Shirabe K, Yamashita Y, Harimoto N, Tsujita E, Takeishi K, *et al*. Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma: a retrospective analysis. *Ann Surg* 2013; **258**:301–305.
28 Sukato DC, Tohme S, Chalhoub D, Han K, Zajko A, Amesur N, *et al*. The prognostic role of neutrophil-to-lymphocyte ratio in patients with unresectable hepatocellular carcinoma treated with radioembolization. *J Vasc Interv Radiol* 2015; **26**:816–24.e1.
29 D'Emic N, Engelman A, Molitoris J, Hanlon A, Sharma NK, Moeslein FM, Chuong MD. Prognostic significance of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients treated with selective internal radiation therapy. *J Gastrointest Oncol* 2016; **7**:269–277.
30 Taussig MD, Irene Koran ME, Mouli SK, Ahmad A, Geevarghese S, Baker JC, *et al*. Neutrophil to lymphocyte ratio predicts disease progression following intra-arterial therapy of hepatocellular carcinoma. *HPB (Oxford)* 2017; **19**:458–464.

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