World J Surg (2019) 43:2587–2594
https://doi.org/10.1007/s00268-019-05051-6

ORIGINAL SCIENTIFIC REPORT

Preoperative Predictors Including the Role of Inflammatory Indices in Predicting Early Recurrence After Re-resection for Recurrent Hepatocellular Carcinoma

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Published online: 20 June 2019

Abstract

Background Repeat liver resection (RLR) for recurrent HCC (rHCC) is a widely accepted treatment modality. However, early recurrence rate is high, frequently resulting in futile resection. We performed this study to evaluate preoperative factors, including the value of inflammatory indices, in predicting early (<1 year) recurrence in patients who underwent RLR for rHCC. This may help clinicians better select patients for RLR, while excluding cases in which RLR for rHCC would likely be futile.

Methods This is a retrospective study of 80 patients where 90 operative cases of RLR and 84 cases of early recurrence (<1 year) post-RLR were evaluated. Preoperative predictors of early recurrence and overall survival (OS) were assessed.

Results There were 31 (34.4%) early recurrences with a 5-year OS of 38.9%. Elevated platelet-to-lymphocyte ratio (PLR) >103.6 was a significant independent preoperative predictor of both early recurrence, relative risk (RR) 4.284 ($P = 0.001$) and OS, RR 2.139 ($P = 0.027$), while alphafetoprotein (AFP) $\geq$ 200 was a significant independent preoperative predictor of early recurrence only, RR 11.655 ($P = 0.030$). Patients were followed-up at a median of 14.3 months with 54.8% developing intrahepatic recurrences and 19.4% developing extrahepatic recurrences.

Conclusion Both, elevated PLR and AFP $\geq$ 200 were independent predictors of early (<1 year) recurrence after RLR for rHCC, while only an elevated PLR was an independent preoperative prognosticators of overall survival. Indication for RLR should be carefully discussed in patients with relapsed HCC with an elevated PLR, due to the potential of early recurrence and poor overall survival.

Introduction

Survival prospects of hepatocellular carcinoma (HCC) remain dismal with up to 76% [1, 2] of patients developing tumour recurrences after curative resection. While the option of liver transplantation exists, it is greatly limited by the availability of technical expertise, scarce liver grafts and a myriad of factors determining patient suitability for transplant. Liver resection continues to be the favoured method of curative treatment wherever possible, but is hampered by high recurrence rates and possible inadequacy of future liver remnant.

Repeat liver resection (RLR) is a well-accepted treatment modality for recurrent HCC (rHCC). However, the decision for RLR for recurrent HCC has to consider the longevity of benefits reaped given the risks of operative morbidity and mortality. Early recurrence after RLR for rHCC is not an infrequent event often resulting in futile surgery. Hence, determination of preoperative predictors of

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early recurrence is important for clinicians to select appropriate patients with rHCC for RLR.

Various indices including alphafetoprotein (AFP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and prognostic nutrition index (PNI) have emerged as potential prognosticators of post-operative outcomes. Elevated AFP, NLR and PLR as well as low PNI have been reported to correlate with greater risks of recurrence and were adverse predictors of recurrence-free survival (RFS) and overall survival (OS) [2–9]. However, to the best of our knowledge; preoperative inflammatory indices have not been studied as preoperative predictors of oncological outcomes after RLR of rHCCs.

Hence, we performed this study with the primary objective of evaluating preoperative factors, including the value of inflammatory indices, in predicting early (<1 year) recurrence in patients who have undergone RLR for rHCC. This may help clinicians better select patients for RLR, while excluding cases in which RLR for rHCC will likely be futile.

Materials and methods

Between 2000 and 2017, 80 consecutive patients who underwent RLR for rHCC at the Singapore General Hospital were identified. A total of 90 cases of RLR were performed with 8 individuals undergoing 2 re-resections and 1 patient with 3 re-resections. Institutional review board approval was obtained prior to conducting the study.

Patients' clinicopathological details were retrieved retrospectively from the computerised clinical and operative databases (Sunrise Clinical Manager version 5.8, Eclipsys Corporation, Atlanta, Georgia, USA, and OTM 10, IBM, Armonk, New York, USA). Their charts were reviewed for supplemental data where necessary. Preoperative data were collected closest to date of resection, and included haematological and biochemical tests (complete blood count, renal and liver function tests, coagulation profile and serum AFP) as well as imaging via computed tomography (CT) and/or magnetic resonance imaging (MRI).

Diagnoses of HCC and their recurrences were made based on imaging findings, the presence of risk factors and/or serum AFP. None of the patients underwent preoperative biopsy for HCC confirmation.

Definitions

Re-resected cases were considered when patients, who had developed a second (or more) HCC recurrence, underwent a repeated liver resection of curative intent. Major hepatic resection referred to the resection of three or more liver segments [10]. Post-operative 30-day/in-hospital and 90-day/in-hospital mortality were defined as deaths occurring within 30 and 90 days, respectively, of surgery or the same hospitalisation. Overall survival was determined from the point of resection till death. Early recurrence referred to intrahepatic and/or extrahepatic recurrences, identified radiologically and/or clinically, within 1 year of RLR for rHCC. R0 resection referred to any microscopically clear resection with a margin >1 mm, while R1 resection was defined as any resection margin ≤1 mm.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social sciences software for Windows, version 20.0 (SPSS Inc., Chicago, IL). Categorical data were analysed via Chi-square test or Fisher's exact test as appropriate, while continuous data were presented as median (range) and analysed via the Mann–Whitney U test. All survival times were calculated from time of surgery. Data for OS were censored at the time of last follow-up if death has not occurred. Five-year OS was analysed via the Kaplan–Meier method.

Formulations for the various indices are as follows: (1) NLR = absolute neutrophil count (μL) divided by absolute lymphocyte count (μL) (2) PLR = absolute platelet count (μL) divided by absolute lymphocyte count (μL) (3) PNI = albumin (g/L) + 0.005 × absolute lymphocyte count (μL) [7, 8]. Receiver operating characteristic (ROC) curves were plotted and the Youden index employed in determining optimal cut-off values for AFP, NLR, PLR and PNI. Cases were then stratified into high or low NLR, PLR and PNI based on the optimal estimates. A value of $P < 0.05$ was considered statistically significant. Six patients who died within a year post-RLR with no tumour recurrences were excluded from the ROC estimations. Univariate analysis of variables identified factors that achieved statistical significance ($P < 0.05$) which were further assessed via multivariate analysis using the stepwise forward Cox regression model.

Results

Applying the ROC curves and Youden index for early recurrence, the optimal cut-off estimates of AFP, NLR, PLR and PNI were 7.9 ng/mL, 2.815, 103.6 and 41.2, respectively. All optimal values are statistically significant.

Clinicopathological features of 90 operative cases for recurrence HCC

Table 1 illustrates variables of the entire cohort as well as stratified comparisons between high or low NLR, PLR and PNI. Median age of the overall cohort was 64 years with a

Table 1 Clinicopathologic features of 90 operative cases for recurrent HCC, stratified by pre-operative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and prognostic nutrition index (PNI)

Variables	Overall (n = 90)	Low NLR (n = 62)	High NLR (n = 28)	P value	Low PLR (n = 42)	High PLR (n = 48)	P value	Low PNI (n = 9)	High PNI (n = 81)	P value
Median age (range), years	64 (34–83)	64 (44–83)	64 (34–80)	0.959	63 (39–83)	64 (34–83)	0.555	62.5 (56–68)	64 (34–83)	0.792
Male gender, n (%)	79 (87.8)	53 (85.5)	26 (92.9)	0.492	36 (85.7)	43 (89.6)	0.749	6 (66.7)	73 (90.1)	0.077
Aetiology										
Hepatitis B, n (%)	66 (73.3)	44 (66.7)	22 (78.6)	0.608	30 (71.4)	36 (75)	0.812	6 (66.7)	60 (74.1)	0.696
Hepatitis C, n (%)	7 (7.8)	7 (11.3)	0	0.094	5 (11.9)	2 (4.2)	0.245	2 (22.2)	5 (6.2)	0.144
Non–B/C, n (%)	16 (17.8)	11 (17.7)	5 (17.9)	1.000	7 (16.7)	9 (18.8)	1.000	1 (11.1)	15 (18.5)	1.000
$2^{nd}/3^{rd}$ recurrence	10 (11.1)	8 (12.9)	2 (7.7)	0.718	7 (17.1)	3 (6.1)	0.179	0	10 (12.3)	0.590
Median AFP (range), ng/mL	5.3 (0.6–51,000)	5.7 (0.6–27,016)	5 (1.6–51,000)	0.731	5.4 (1.4–27,016)	5.2 (0.6–51,000)	0.846	9.9 (1.9–8826)	5.3 (0.6–51,000)	0.958
Median tumour size (range), cm	2.3 (0.6–20)	2.6 (0.6–12.5)	2.3 (1–20)	0.773	2.4 (0.6–6.8)	2.5 (0.9–20)	0.402	2.5 (1.2–12.5)	2.5 (0.6–20)	0.437
Major hepatic resection (%)	13 (14.4)	8 (12.9)	5 (17.9)	0.533	4 (9.5)	9 (18.8)	0.245	3 (33.3)	10 (12.3)	0.119
Anatomical resection (%)	25 (27.8)	20 (32.2)	5 (17.9)	0.207	12 (28.6)	13 (27.1)	1.000	3 (33.3)	22 (27.2)	0.704
Tumour rupture, n (%)	4 (4.4)	3 (4.8)	1 (3.6)	1.000	1 (2.4)	3 (6.2)	0.620	0	4 (4.9)	1.000
Cirrhosis, n (%)	59 (65.6)	44 (71)	15 (53.6)	0.150	30 (71.4)	29 (60.4)	0.374	8 (88.9)	51 (63.0)	0.156
Macrovascular involvement, n (%)	4 (4.4)	2 (3.2)	2 (7.1)	0.586	2 (4.8)	2 (4.2)	1.000	1 (11.1)	3 (3.7)	0.349
R1 resection, n (%)	20 (22.2)	13 (21)	7 (25)	0.785	11 (26.2)	9 (18.8)	0.452	1 (11.1)	19 (23.5)	0.677
High tumour grade, n (%)	41 (45.6)	27 (43.5)	14 (50)	0.650	17 (40.5)	24 (50)	0.402	4 (44.4)	37 (45.7)	1.000
Satellite nodules, n (%)	6 (6.7)	4 (6.5)	2 (7.1)	1.000	3 (7.1)	3 (6.2)	1.000	1 (11.1)	5 (6.2)	0.479
Multinodular histology, n (%)	16 (17.8)	10 (16.1)	6 (21.4)	0.561	5 (11.9)	11 (22.9)	0.269	2 (22.2)	14 (17.3)	0.659
Median DFI to last reresection (range), months	20.0 (4.2–163.8)	17.7 (4.2–117.5)	26.1 (7.2–163.8)	0.324	21.5 (10.2–117.5)	19 (4.2–163.8)	0.147	16 (8.9–91.7)	20.8 (4.2–163.8)	0.378

AFP alphafetoprotein, *DFI* disease free interval

Table 2 Univariate and multivariate analysis of predictive factors of early (<1 year) recurrence in 84 operative cases with recurrent HCC

Variables	Overall (n = 84)	Univariate		Multivariate	
		RR (95% CI)	P value	RR (95% CI)	P value
Categorical	n (%)				
Age > 70 years old	18 (21.4)	1.468 (0.632–3.411)	0.372		
Male gender	73 (13.1)	1.098 (0.384–3.145)	0.861		
Hepatitis B	63 (75)	1.809 (0.632–5.181)	0.269		
Hepatitis C	6 (7.1)	1.224 (0.167–8.988)	0.843		
Non-hepatitis B/C	14 (16.7)	0.552 (0.167–1.818)	0.328		
2nd/3rd recurrence	10 (11.9)	1.094 (0.333–3.602)	0.882		
Tumour > 3 cm	31(36.9)	1.295 (0.640–2.622)	0.472		
Tumour > 5 cm	13 (15.5)	1.371 (0.562–3.347)	0.488		
Tumour rupture	4 (4.8)	1.694 (0.402–7.136)	0.472		
Major hepatic resection	12 (14.3)	0.611 (0.186–2.012)	0.418		
Anatomical resection	24 (28.6)	0.503 (0.176–1.439)	0.200		
Macrovascular involvement	4 (4.8)	3.147 (0.950–10.426)	0.061		
High NLR	26 (31)	1.869 (0.922–3.786)	0.083		
High PLR	45 (53.6)	4.359 (1.869–10.168)	**0.001**	4.284 (1.826–10.048)	**0.001**
High PNI	76 (90.5)	1.558 (0.372–6.534)	0.544		
AFP > 200 ng/mL	10 (11.9)	3.533 (1.495–8.352)	**0.004**	11.655 (1.276–106.441)	**0.030**
AFP > 400 ng/mL	9 (10.7)	2.987 (1.207–7.392)	**0.018**	0.278 (0.028–2.758)	0.274

Continuous	Median (range)	Univariate	
		RR (95% CI)	P value
Albumin (g/L)	39.5 (29–49)	0.971 (0.892–1.058)	0.508
Creatinine (μmol/L)	87 (47–594)	0.989 (0.973–1.005)	0.188
Platelet ($\times 10^9$/L)	174 (56–415)	1.003 (0.998–1.008)	0.204
Neutrophil count ($\times 10^9$/L)	3.27 (1.23–8.71)	1.078 (0.816–1.424)	0.598
DFI (months) to last reresection	20.8 (4.2–163.8)	0.996 (0.979–1.005)	0.245

NLR neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *PNI* prognostic nutrition index, *AFP* alphafetoprotein, *DFI* disease free interval

Bold values indicate statistical significance ($P < 0.05$)

greater proportion of male patients (79%), those afflicted with hepatitis B (73.3%) and cirrhotic livers (65.6%). Amongst the 90 RLR cases, 13 (14.4%) were major hepatic resections, 25 (27.8%) underwent anatomical resections, and 10 (11.1%) cases were a second or third repeated resection. Twenty patients (22.2%) had R1 resections which may be associated with a higher proportion of patients with non-anatomical resections. Due to the presence of cirrhosis inadequate future liver remnant (FLR), frequently, non-anatomical parenchyma-saving resections were performed to preserve FLR. Patient demographics were similar across the board, and there was no significant difference between the listed variables and stratified groups.

The 30-day/in-hospital and 90-day/in-hospital mortality was 4.4% (4 patients) and 6.7% (6 patients), respectively. Reasons for 30-day post-operative demise included acute myocardial infarct (n = 2), cerebrovascular accident (n = 1) and pneumonia (n = 1). Liver decompensation (n = 1) and demise from recurrent advanced HCC (n = 1) contributed to the 90-day mortality in this series. At the time of analysis, 65% (n = 52) of patients developed tumour recurrence and 46.3% (n = 37) had demised. Median OS was 41.1 months (interquartile range 22.0–91.0 months) with a 5-year OS of 38.9%.

Predictive factors of early recurrence (<1 year) and futile surgery

Of the 90 RLR cases, 31 (34.4%) recurred early within a year resulting in futile re-resections. High PLR, AFP > 200 and AFP > 400 were identified as potential prognosticators from univariate analyses with subsequent multivariate analyses demonstrating high PLR (>103.6) and AFP > 200 as independent predictors of early recurrence (Table 2).

Table 3 Univariate and multivariate analysis of prognostic factors of OS in 90 cases of re-resected HCCs

Variables	*n* (%)	Univariate		Multivariate	
		OS HR (95% CI)	*P* value	OS HR (95% CI)	*P* value
Categorical					
Age > 70	19 (21.1)	1.413 (0.634–3.150)	0.398		
Male gender	11 (12.2)	1.872 (0.816–4.291)	0.139		
Hepatitis B	66 (73.3)	1.411 (0.618–3.222)	0.414		
Hepatitis C	7 (7.8)	0.944 (0.325–3.457)	0.924		
Non-B/C	16 (17.8)	0.690 (0.244–1.954)	0.485		
2nd/3rd recurrence	10 (11.1)	0.565 (0.172–1.850)	0.345		
Tumour > 3 cm	34 (37.8)	1.077 (0.554–2.094)	0.827		
Tumour > 5 cm	13 (14.4)	1.313 (0.546–3.156)	0.543		
Tumour rupture	4 (4.4)	2.052 (0.281–15.005)	0.479		
Major hepatic resection	25 (27.8)	0.750 (0.265–2.121)	0.588		
Anatomical resection	13 (14.4)	0.387 (0.151–0.994)	**0.048**	0.3983 (0.155–1.022)	0.056
Macrovascular involvement	4 (4.4)	2.205 (0.671–7.242)	0.193		
High NLR	28 (31.1)	1.846 (0.962–3.541)	0.065		
High PLR	48 (53.3)	2.193 (1.116–4.310)	**0.023**	2.139 (1.091–4.196)	**0.027**
High PNI	81 (90)	0.518 (0.216–1.244)	0.141		
AFP > 200 ng/mL	12 (13.3)	2.048 (0.898–4.675)	0.222		
AFP > 400 ng/mL	11 (12.2)	1.763 (0.734–4.234)	0.204		

Continuous	Median (range)	Univariate	
		OS HR (95% CI)	*P* value
Albumin (g/L)	39.5 (29–49)	0.936 (0.865–1.013)	0.101
Creatinine (μmol/L)	87.4 (47–594)	1.003 (0.998–1.007)	0.233
Platelet ($\times 10^9$/L)	174 (56–415)	1.001 (0.996–1.005)	0.799
Neutrophil count ($\times 10^9$/L)	3.29 (1.19–8.71)	1.026 (0.806–1.305)	0.835
DFI (months) to last reresection	20 (4.2–163.8)	0.987 (0.972–1.002)	0.082

NLR neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *PNI* prognostic nutrition index, *AFP* alphafetoprotein, *DFI* disease free interval

Bold values indicate statistical significance ($P < 0.05$)

Table 4 Early tumour recurrence 1 year post repeat liver resection

Recurrence site	Cases with early recurrence (%)
Intrahepatic	17/31 (54.8%)
Extrahepatic	6/31 (19.4%)
Intra and extrahepatic	8/31 (25.8%)

Prognostic factors of OS

Preoperative variables were assessed via univariate analyses, with anatomical resection and high PLR, shown to be statistically significant prognosticators of OS (Table 3). On multivariate analysis, only high PLR was a significant prognostic factor of OS.

Follow-up

At the time of study conclusion, the patients had a median follow-up of 14.3 months (0–154.6 months). The follow-up was more than 1 year after all 84 RLR (excluding the 6 early post-operative mortalities).

Of the 31 cases with early tumour recurrences, majority (54.8%) developed intrahepatic tumours, 6 patients had extrahepatic metastases while 8 individuals had both intrahepatic and extrahepatic recurrences (Table 4).

Discussion

In the face of pervasive hepatitis and liver cirrhosis, tumour recurrence remains the rate-limiting factor of survival in patients with HCCs. Consequently, RLR and salvage liver

transplantation received increasing focus as curative treatments for rHCC [11]. While primary liver transplantation has proven to have superior OS and recurrence-free survival relative to liver resection, it is restricted by the availability of liver grafts [12, 13]. RLR thus remains the predominant intervention offering potential cure for patients with tumour recurrences in many countries, especially Asia [14]. However, hepatic resections are not without its associated risks of morbidity and mortality. The prospects of threatened remnant liver function with poor 5-year RFS of 10–17% after RLR question the utility of the procedure [15, 16]. Hence, there is a critical need for proper preoperative risk stratification in patients with rHCC being considered for potential RLR to avoid or reduce the incidence of futile resections. This information would also be of great importance for clinicians during preoperative counselling of patients, prior to these procedures, which are associated with significant morbidity and mortality [17]. In this study, we found that a high PLR and AFP were independent predictors of early recurrence.

As a glycoprotein expressed during hepatocyte regeneration, AFP is the most commonly used tumour marker for HCC but has low sensitivity which limits its diagnostic accuracy [18–20]. Its application has been shown in extending to tumour prognostication, as numerous studies have identified the utility of elevated AFP in predicting HCC recurrence after initial hepatic resection [2, 3]. On the other hand, other investigators have disputed its prognostic role for survival and recurrence for recurrent tumours post-RLR [21–23]. It is important to note that a large heterogeneity exists between these studies with variable AFP cut-off values used, ranging between 32 and 400 ng/mL with unsurprisingly conflicting results. In this study, while our optimal AFP estimate was 7.9 ng/mL, it would be more practical to utilise commonly accepted cut-off values of 200 and 400 ng/mL. Elevated AFP $>$ 200 ng/mL but not $>$ 400 ng/mL was shown to be a statistically significant independent predictor of early recurrence (Table 2).

Inflammatory indices such as PLR, NLR and PNI, which are derived from markers of systemic inflammation, have been shown to exhibit propensities for aggressive tumour behaviours [24, 25]. Inflammatory markers (i.e. platelets, lymphocytes, neutrophils) are linked with cytokine production, tumour cell proliferation, muted anti-tumoural responses and increased extravasation into the extracellular matrix resulting in metastases [24–26]. There are multiple studies to date investigating the predictive impact of inflammatory indices with varying conclusions amongst differing groups and confounding elements. For example, although PLR has been repeatedly shown to prognosticate HCC, its optimal cut-off value remains undefined, reportedly ranging widely between 96.13 and 300 [27–29]. In this study, a high PLR ($>$ 103.6) was a significant independent predictor for both OS and early recurrence. However, neither NLR nor PNI was a significant prognosticator for OS and early recurrence. The PLR cut-off in this study was consistent with that reported by previous authors [9, 27, 28].

The role of NLR in the prognostication of HCC remains controversial. Several authors have demonstrated NLR to be an independent predictor for survival outcomes and early recurrence [5, 30–32], while others failed to demonstrate its prognostic value [7, 33, 34]. Similarly, the role of PNI also remains controversial with some studies supporting its role in HCC prognostication [7, 8, 35] and others refuting its claims [32, 34]. Moreover, these studies have largely focused on survival outcomes after primary hepatic resections rather than RLR for rHCC, with significant variability in their respective cohorts and different optimal cut-off values. Hence, the value of applying these inflammatory indices as preoperative predictors of early recurrence after RLR for rHCC remains poorly defined.

The results of the present study are limited by its retrospective nature and relatively small sample size. The small cohort size could have resulted in type 1 or 2 errors resulting in the inability to detect a statistical significance in the role of NLR and PNI in prognosticating rHCC after RLR. There was also significant variability in the number of cases between low- and high-PNI groups as well, undermining objective comparisons of the patient groups (Table 1). Thirdly, as there were no standardised uniformly accepted cut-offs for the inflammatory indices, these cut-offs were calculated from our own patient cohort and have not been validated. However, this study to our knowledge is the first to demonstrate the importance of PLR has a preoperative predictor of early recurrence in patients undergoing RLR for rHCC. This information is especially important for clinicians when counselling patients preoperatively prior to surgery.

In conclusion, elevated PLR and AFP $\geq$ 200 were independent predictors of early ($<$1 year) recurrence after RLR for rHCC, while only an elevated PLR was an independent preoperative prognosticator of overall survival. Indication for RLR should be carefully discussed in relapsed HCC with elevated PLR, due to the potential of early recurrence and poor overall survival.

Compliance with ethical standards

Conflict of interest All authors have no conflict of interest and declarations

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