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ORIGINAL ARTICLE

Association between neutrophil–lymphocyte ratio, socioeconomic status, and ethnic minority with treatment outcome in hepatocellular carcinoma

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Abstract

Background Patients with lower socioeconomic status (SES), ethnic minorities and elevated neutrophil–lymphocyte ratio (NLR) have been suggested to have worse outcomes in hepatocellular carcinoma (HCC). However, how changes in NLR after intervention relate to survival has not been elucidated.

Objectives We evaluated the association of NLR with overall survival (OS) and progression-free survival (PFS) in a large institutional cohort of HCC.

Methods We reviewed all patients diagnosed with HCC between 2005–2016. The association between elevated NLR (> 4) and survival was examined with univariable and multivariable Cox regression.

Results We identified 991 patients diagnosed with HCC. Lower SES and Hispanic and non-Hispanic Black ethnicity were significantly associated with lower NLR ($p = 0.015$ and 0.019, respectively). Elevated NLR, but not SES or ethnicity, was an independent predictor of worse OS (HR = 1.66, $p < 0.001$) and PFS (HR = 1.25, $p = 0.032$). The median OS in patients with elevated NLR was 8 months, compared to 42 months in patients with normal NLR. Patients with elevated NLR unresponsive to treatment and those with NLR that became elevated after treatment had significantly worse 3-year OS (47% and 44%, respectively), compared to patients whose NLR remained normal or normalized after treatment (72% and 80%, respectively; $p < 0.01$).

Conclusions Our study showed that elevated NLR, but not SES or ethnicity, is an independent prognostic marker for OS and PFS in patients with HCC. NLR trends following intervention were highly predictive of outcome. NLR is easy to obtain and would provide valuable information to clinicians in evaluating prognosis and monitoring response after procedures.

Keywords Hepatocellular carcinoma · Socioeconomic status · Ethnicity · Neutrophil-to-lymphocyte ratio · Prognosis

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cause of cancer worldwide, and the leading cause of cancer-related deaths. The incidence is increasing worldwide, and in the US it has more than tripled since 1980 [1]. Despite the many advances in treatments for HCC, the 5-year survival rate remains less than 15% [2]. Although there have been many systems proposed in staging HCC, it is still controversial what the most important prognostic factors are. Blood biomarkers that can serve as prognostic tools for survival and metastatic recurrence would be valuable in helping clinicians decide on the best therapeutic option.

Inflammation affects cancer progression in numerous ways, including damage to cell DNA, tumor cell motility and

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invasion, and promotion of angiogenesis [3]. Recent studies have shown increasing evidence that increased systemic inflammation leads to poor cancer-specific survival [4]. Various markers of systemic inflammatory response, such as C-reactive protein (CRP), absolute neutrophil or lymphocyte count, and neutrophil-to-lymphocyte ratio (NLR), have been investigated. NLR, in particular, was associated with tumor progression and survival in many cancers, including breast cancer [5], esophageal cancer [6], colorectal cancer [7], and gastric cancer [8].

For HCC, however, studies investigating the role of NLR in predicting overall and post-therapeutic survival have yielded inconsistent results. While some studies show that elevated NLR is associated with worse overall survival (OS) and progression-free survival (PFS), others did not support the same finding. It has been reported that NLR was not a significant predictor of OS on multivariable analysis, with inferior prognostic value compared to other inflammatory markers [9]. In addition, fewer studies were done in North America compared to Europe and Asia, and findings supporting NLR as a prognostic factor have not been as strong in North American populations [10]. Differences in study design and population size also warrant stronger evidence from large-sample studies.

In addition, patients with lower socioeconomic status (SES) and ethnic minorities have been suggested to have worse outcomes in HCC [11–13], likely from more advanced disease presentation and more patients receiving palliative treatment. There have not been many studies on factors that impact NLR. In particular, it is unclear if factors such as SES and ethnicity play a role in modulating NLR. The only study investigating the association between these factors was performed in healthy participants and found that Black and Hispanic people had significantly lower mean NLR values compared to those who were White and that SES was inversely associated with NLR [14].

Using a large urban medical center single institutional cohort of patients with HCC, we investigated the association of NLR at diagnosis with OS and PFS, as well as how changes in NLR after intervention were associated with outcome. We also examined the relationship of NLR with other variables including SES and ethnicity.

Methods

Patient selection

In this Institutional Review Board-approved study, we utilized a database from an urban medical center to identify all patients diagnosed with HCC, either based on histology or imaging criteria diagnostic of HCC, in the years 2005 to 2016. Patients with HCC who were diagnosed and treated elsewhere were excluded. The patient flow diagram is shown in Supplementary Fig. 1.

Definitions and data extraction

The laboratory results such as NLR, alpha fetoprotein (AFP), and those needed for the calculation of Model for End-Stage Liver Disease (MELD) and Child–Turcotte–Pugh scores were obtained from the first blood samples drawn after the initial diagnosis. NLR was calculated based on complete blood count, by dividing the absolute neutrophil count by the absolute lymphocyte count. All of the NLRs available in the system in the first 3 years following diagnosis were collected. NLR data points were excluded if the patient was febrile around the time of collection. SES was represented by a summary score that took into account the median household income, the median value of housing units, education and occupation of inhabitants, and the percentage of households receiving interest or net rental income [15]. Staging was derived based on American Joint Committee on Cancer system that scores tumor size, lymph nodes affected, and metastases (AJCC TNM).

Four groups of patients were defined based on the NLR collected before and after the first intervention. The first intervention represents the first time patients received treatment for HCC and can be chemotherapy, transarterial chemoembolization (TACE), resection, radiofrequency ablation (RFA), or transplant. Treatments documented to be for comfort care were defined as palliative intent, with all others considered HCC-directed therapies. We defined pre-intervention NLR as within 3 to 45 days before first intervention and post-intervention as within 10 to 90 days after the intervention. We used NLR at least 10 days after the procedure to minimize the effect of the post-intervention inflammatory syndrome. Patients were stratified as those with normal NLR at diagnosis (defined as ≤ 4.0) that remained normal after the intervention, those with elevated NLR at diagnosis that remained elevated after the intervention, those with normal NLR at diagnosis that subsequently became elevated after the intervention, and those with elevated NLR at diagnosis that normalized after the intervention.

OS was defined as the interval between diagnosis and death or censored at last time of contact. PFS was defined as the interval between diagnosis and progression of disease or death due to any cause or otherwise censored at last time of contact.

Statistical analysis

Cox proportional hazards regression analyses were used to evaluate the independent association between elevated NLR and OS as well as PFS. Bivariate associations between elevated NLR and clinical patient characteristics were

examined after assessing normality and equal variance assumptions for continuous variables.

Univariable and multivariable Cox models were generated for OS and PFS based on elevated NLR and patient characteristics associated with survival. Multivariable models were generated based on including all variables with $p < 0.1$ on univariable survival analysis and then reducing the model to eliminate issues with multicollinearity between variables explaining a large part of the same variance in OS and PFS. The final models were determined using backwards elimination of any variables with $p \geq 0.05$ in the multivariable analyses.

The proportional hazards assumptions were assessed for the final multivariable models by formal test and visual inspection of Schoenfeld residuals for each model covariate.

Sensitivity analyses were performed using varying definitions of elevated NLR in the final multivariable model to determine how dependent the association with OS is on the choice of NLR cut-off. All statistical analyses were performed using STATA v.14 (StataCorp, College Station, TX).

Results

Patient demographics

We identified 991 patients diagnosed with HCC between 2005 and 2016 that met inclusion criteria with clinical features reported in Table 1. The mean age was 63.6 years and the majority were male ($n = 713$, 72%). The median score representing SES in the cohort was − 2.81. Of patients with known ethnicity, 332 were Hispanic, 242 non-Hispanic black, 106 non-Hispanic white, and 18 were Asian. In regards to etiology of HCC, 623 patients had hepatitis C alone (69%), 65 patients had hepatitis B alone (7%), 21 had concurrent hepatitis B and C (2%). About half of the patients were classified with Child–Turcotte–Pugh Class A ($n = 478$, 49%), with 371 classified as Child–Turcotte–Pugh Class B (38%), and 121 as Child–Turcotte–Pugh Class C (13%). The median MELD score was 11.1 (inter-quartile range: 8.5–16). Most of the patients had a single tumor ($n = 544$, 63%). For treatment, 689 patients received HCC-directed therapies (71%), while 100 patients received palliative therapies (10%); for 188 patients no treatment information was found in their chart.

NLR at diagnosis

263 patients were found to have elevated NLR, defined as NLR > 4.0. The cut-off of 4.0 was chosen as it has been presented as clinically relevant in previous studies [16], and here we attempt to validate this in an independent patient cohort. Patients with elevated NLR had more advanced cancer stage, greater maximal tumor diameter, worse MELD and Child–Turcotte–Pugh Score, and more frequent occurrences of portal vein thrombosis (Table 1). For those with known ethnicity, Hispanics were more likely to present with earlier stage disease compared to non-Hispanic whites and non-Hispanic blacks, who had a higher prevalence of more advanced disease stage. NLR was significantly associated with ethnicity ($p = 0.019$) and SES ($p = 0.015$) on univariable analysis. Non-Hispanic white patients and those with an ethnicity reported as declined/unknown/other were more likely to have elevated NLR, compared to Hispanics and non-Hispanic black patients. After controlling for disease stage, however, the association between ethnicity and NLR was no longer significant. Higher SES was associated with higher NLR when analyzed based on quartiles of SES. This association persists after controlling for stage but is only borderline significant ($p = 0.073$). Furthermore, the mean SES for patients with normal NLR was -3.51 ± 0.11 compared to -3.00 ± 0.17 for those with elevated NLR ($p = 0.014$).

Outcomes

The median follow-up was 14.9 months, and 496 patients had died. Median OS for the entire cohort was 32 months, median PFS was 8.3 months and median OS for stage I, II, III and IV patients was 87.7 months, 54.8 months, 11.3 months, and 3.1 months, respectively.

The results of the univariable Cox regression analyses are summarized in Table 2. Elevated NLR was associated with worse OS (HR = 2.16, 95% CI: 1.79–2.61, $p < 0.001$). Higher stage, MELD score, AFP, Child–Turcotte–Pugh Class, number of tumors, larger tumor size, presence of distant metastasis and presence of portal vein thrombosis were also significantly associated with worse OS. Being Hispanic was associated with better OS compared to being non-Hispanic White, whereas declined/unknown/other ethnicity was associated with worse OS and PFS. Age, gender and SES were not significantly associated with OS. Female gender was associated with slightly better PFS in univariable analysis.

Results of the multivariable analysis for predictors of OS and PFS are summarized in Table 3. Patients who received palliative treatments were excluded from the multivariate survival analysis as they died rapidly after diagnosis and including them would severely violate the proportional hazards assumption. Child–Turcotte–Pugh score was not included since most of the same variance is explained by MELD score. Similarly, stage and AFP were not included since most of this variance is explained by the number of tumors. Out of the 881 patients who received non-palliative treatments, 592 had complete data for inclusion in the multivariable Cox regression (164 patients were missing maximum tumor diameter, 26 missing MELD, 14 missing NLR, 121 missing number of tumors, and 87

Table 1 Baseline characteristics of patients

Patient characteristics	All patients ($n=991$)	Normal NLR (≤ 4.0) ($n=714$)	Elevated NLR (>4.0) ($n=263$)	p value
Age (year), mean ± SD	63.6 ± 10.7	63.4 ± 10.5	64.2 ± 11.4	0.31
Gender *n* (%)				
Male	713 (72)	507 (71)	196 (75)	0.28
Female	278 (28)	207 (29)	67 (25)	
Stage *n* (%)				
I	329 (38)	275 (43)	54 (25)	
II	219 (25)	184 (28)	35 (16)	**< 0.001**
III	226 (26)	138 (21)	88 (40)	
IV	99 (12)	57 (8)	42 (19)	
Treatment indication				
Curative	689 (71)	547 (77)	142 (54)	
Palliative	100 (10)	55 (8)	45 (17)	**< 0.001**
No info	188 (19)	112 (15)	76 (29)	
Maximum tumor diameter (cm), median (IQR)	3.0 (1.9–5.4)	2.8 (1.8–4.9)	4.5 (2.4–7.8)	**< 0.001**
MELD score, median (IQR)	11.1 (8.5–16.0)	10.2 (8.2–14.1)	14.7 (10.3–20.8)	**< 0.001**
AFP (ng/ml), median (IQR)	31.4 (7.0–489)	25.9 (7.1–277)	79.1 (6.7–2985)	**0.016**
NLR, median (IQR)	2.53 (1.57–4.30)	2.00 (1.33–2.75)	6.29 (5.00–10.0)	**< 0.001**
Child–Pugh category *n* (%)				
A	478 (49)	410 (58)	68 (26)	
B	371 (38)	237 (33)	134 (51)	**< 0.001**
C	121 (13)	60 (9)	61 (23)	
Number of tumors *n* (%)				
1	544 (63)	411 (64)	133 (60)	
2–3	165 (19)	135 (21)	30 (14)	**< 0.001**
> 3	153 (18)	95 (15)	58 (26)	
Race/ethnicity *n* (%)				
Non-hispanic white	106 (11)	72 (10)	34 (13)	
Hispanic	332 (34)	255 (36)	77 (29)	
Non-hispanic black	242 (25)	188 (26)	54 (21)	**0.019**
Asian	18 (2)	12 (2)	6 (2)	
Declined/unknown/other	277 (28)	186 (26)	91 (35)	
Hepatitis status *n* (%)				
Negative	189 (21)	121 (18)	68 (30)	
Hep B	65 (7)	49 (7)	16 (7)	**0.004**
Hep C	623 (69)	481 (72)	142 (61)	
Hep B and C	21 (2)	16 (2)	5 (2)	
Distant metastasis at dx *n* (%)				
No	932 (95)	687 (95)	245 (93)	**0.043**
Yes	45 (5)	27 (5)	18 (7)	
Portal vein thrombosis *n* (%)				
No	825 (84)	625 (88)	200 (76)	**< 0.001**
Yes	152 (16)	89 (12)	63 (24)	

Bold value indicates $p < 0.05$

NLR Neutrophil lymphocyte ratio, *MELD* model for end-stage liver disease, *AFP* alpha-fetoprotein

missing hepatitis status, and for some patients several of these data points were missing). Table 3 shows that elevated NLR is an independent predictor of OS (HR 1.66, 95% CI: 1.28–2.15, $p < 0.001$) and PFS (HR = 1.25, 95% CI: 1.02–1.54, $p = 0.032$). Increased tumor diameter, higher MELD score, treatment intent, an increasing

Table 2 Univariable survival analyses of prognostic factors for OS and PFS. Note that columns here represent the association with overall and progression-free survival, respectively

	Overall survival		Progression-free survival	
Univariable cox regression	HR (95% CI)	*p* value	HR (95% CI)	*p* value
NLR (continuous)	1.08 (1.07–1.10)	**< 0.001**	1.06 (1.04–1.07)	**< 0.001**
NLR (> 4.0 vs. ≤ 4.0)	2.16 (1.79–2.61)	**< 0.001**	1.67 (1.44–1.95)	**< 0.001**
Age (per year)	1.007 (0.999–1.016)	0.10	1.005 (0.998–1.012)	0.14
Gender (female vs. male)	0.88 (0.72–1.07)	0.21	0.85 (0.73–0.99)	**0.037**
Stage				
I	Ref		Ref	
II	1.30 (0.99–1.71)	**< 0.001**	1.31 (1.08–1.59)	**< 0.001**
III	3.44 (2.70–4.39)		2.53 (2.10–3.04)	
IV	5.54 (4.14–7.42)		3.98 (3.14–5.05)	
Treatment indication (no info vs. HCC-directed)	3.88 (3.18–4.75)	**< 0.001**	2.00 (1.69–2.35)	**< 0.001**
Maximum tumor diameter (per cm)	1.16 (1.13–1.18)	**< 0.001**	1.13 (1.11–1.15)	**< 0.001**
MELD score (per unit)	1.04 (1.03–1.05)	**< 0.001**	1.03 (1.02–1.04)	**< 0.001**
logAFP (per ln(ng/ml))	1.19 (1.16–1.23)	**< 0.001**	1.15 (1.12–1.18)	**< 0.001**
Child–Turcotte–Pugh category				
A	Ref		Ref	
B	2.05 (1.68–2.49)	**< 0.001**	1.74 (1.50–2.01)	**< 0.001**
C	3.50 (2.70–4.53)		2.13 (1.72–2.64)	
Number of tumors				
1	Ref		Ref	
2–3	1.54 (1.19–1.98)	**< 0.001**	1.52 (1.26–1.83)	**< 0.001**
> 3	2.74 (2.15–3.50)		2.41 (1.99–2.91)	
Race/ethnicity				
Non-hispanic white	Ref		Ref	
Hispanic	0.69 (0.51–0.95)		1.01 (0.79–1.29)	
Non-hispanic black	1.02 (0.74–1.41)	**< 0.001**	1.32 (1.02–1.70)	**< 0.001**
Asian	0.80 (0.38–1.69)		1.06 (0.63–1.78)	
Declined/unknown/other	1.48 (1.10–2.01)		1.43 (1.12–1.83)	
Socioeconomic status				
Lowest quartile	Ref		Ref	0.94
2nd to lowest quartile	1.07 (0.83–1.37)		1.01 (0.84–1.23)	
2nd to highest quartile	0.98 (0.76–1.27)	0.92	0.96 (0.79–1.16)	
Highest quartile	1.03 (0.80–1.33)		0.97 (0.80–1.17)	
Hepatitis status				
Negative	Ref		Ref	
Hep B	0.92 (0.64–1.32)		1.12 (0.83–1.52)	
Hep C	0.52 (0.42–0.64)	**< 0.001**	0.80 (0.67–0.95)	**< 0.001**
Hep B and C	0.71 (0.38–1.32)		1.54 (0.94–2.51)	
Distant metastasis at d*x* (yes vs. no)	1.95 (1.31–2.90)	**0.001**	2.69 (1.97–3.67)	**< 0.001**
Portal vein thrombosis (yes vs. no)	2.32 (1.87–2.88)	**< 0.001**	2.06 (1.72–2.46)	**< 0.001**

Bold value indicates $p < 0.05$

NLR Neutrophil lymphocyte ratio, *MELD* model for end-stage liver disease, *AFP* alpha-fetoprotein

number of tumors and presence of portal vein thrombosis were also significantly associated with worse OS and PFS. Hepatitis status was an independent predictor of PFS but not OS. After adjusting for the disease characteristics mentioned above, patient-related factors such as age, race and ethnicity were no longer significantly associated with outcome, but importantly the association between NLR and OS or PFS did not notably change when removing these covariates from the model.

Patients with elevated NLR had markedly decreased OS compared to those with normal NLR, with 3-year OS at 33.1% compared to 54.6% (Fig. 1).

Table 3 Multivariate analysis of prognostic factors by Cox regression model

Multivariable Cox regression	Overall survival		Progression-free survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
NLR (> 4.0 vs. ≤ 4.0)	1.66 (1.28–2.15)	**< 0.001**	1.25 (1.02–1.54)	**0.032**
Maximum tumor diameter (per cm)	1.14 (1.11–1.17)	**< 0.001**	1.12 (1.09–1.15)	**< 0.001**
MELD score (per unit)	1.02 (1.01–1.03)	**< 0.001**	1.02 (1.01–1.03)	**0.001**
Number of tumors				
1	Ref		Ref	
2–3	1.78 (1.34–2.37)	**< 0.001**	1.74 (1.41–2.15)	
> 3	1.26 (0.90–1.76)		1.66 (1.30–2.13)	
Portal vein thrombosis (yes vs. no)	1.80 (1.33–2.42)	**< 0.001**	1.46 (1.14–1.88)	**0.003**
Treatment indication (no info vs. curative)	2.92 (2.15–3.98)	**< 0.001**	1.72 (1.33–2.23)	**< 0.001**
Hepatitis status				
Negative	–		Ref	
Hep B			1.31 (0.88–1.95)	
Hep C			1.24 (0.98–1.58)	**0.006**
Hep B and C			2.97 (1.60–5.52)	

Bold value indicates $p < 0.05$

NLR Neutrophil lymphocyte ratio, *MELD* model for end-stage liver disease

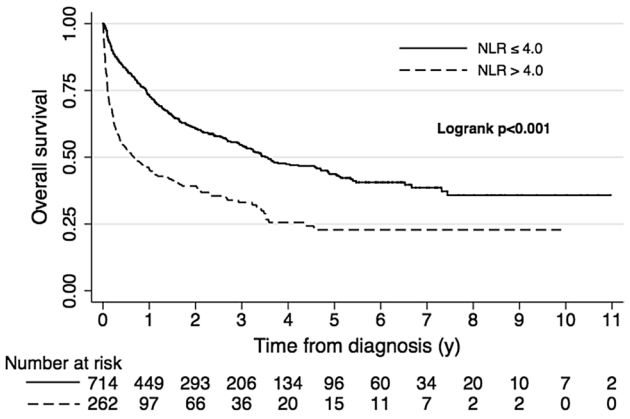

Fig. 1 Overall survival for patients with normal compared to elevated NLR

Table 4 Sensitivity analysis of the NLR cut-off

NLR sensitivity analysis*	HR (95% CI)	Harrell's C
NLR (> 2.0 vs. ≤ 2.0)	1.28 (1.01–1.64)	0.761
NLR (> 3.0 vs. ≤ 3.0)	1.40 (1.10–1.78)	0.760
NLR (> 4.0 vs. ≤ 4.0)	1.66 (1.28–2.15)	0.761
NLR (> 5.0 vs. ≤ 5.0)	1.86 (1.41–2.46)	0.764

*Adjusted for maximum tumor diameter, MELD score, Number of tumors, portal vein thrombosis and treatment indication

A sensitivity analysis of the NLR cut-off using the same multivariable model as in Table 3 is shown in Table 4. Although the hazard ratio increased from 1.28 to 1.86 as the cut-off for NLR increased from 2.0 to 5.0, it remained statistically significant regardless of the chosen cut-off, with $p < 0.05$ for all. Furthermore, analyzing the association of NLR with OS based on tertiles of NLR using the same multivariable model results in HRs of 1.0 (ref), 1.16 and 1.52 for the 1st, 2nd and 3rd teritle, showing a significant linear trend ($p = 0.013$).

Table 5 Distribution of initial intervention stratified by NLR (*n* and %)

	NLR ≤ 4.0		NLR > 4.0	
Non-sorafenib chemo	13	1.8	7	2.7
Surgery	45	6.3	14	5.3
SBRT	13	1.8	2	0.8
RFA	58	8.1	10	3.8
Y-90	31	4.3	7	2.7
Sorafenib	70	9.8	37	14.1
TACE	309	43.3	58	22.0
Transplant	8	1.1	7	2.7
No treatment info	112	15.7	76	28.9
Palliative	55	7.7	45	17.1

NLR subgroup analysis

689 patients underwent a HCC-directed therapy, and the distribution for initial intervention for normal and elevated NLR is shown in Table 5. TACE made up the majority of first-line interventions ($n = 367$), with sorafenib ($n = 107$) and RFA ($n = 68$) being the second and third most common. Of note, patients with elevated NLR were more likely to receive palliative care (17.1%) compared to patients with

normal NLR (7.1%). An exploratory analysis was performed stratifying by first-line treatment intervention. While adjusting for maximum tumor diameter, MELD score, number of tumors and portal vein thrombosis, the OS HR for NLR > 4.0 is 1.75 (95% CI: 1.03–2.99, $p = 0.04$) for patients treated with chemotherapy or Sorafenib, 2.51 (95% CI: 0.96–6.56, $p = 0.06$) with radiation therapy or RFA, 1.05 (95% CI: 0.65–1.70, $p = 0.85$) with Yttrium-90 spheres or TACE and 1.05 (95% CI: 0.18–6.15, $p = 0.96$) for those receiving hepatectomy or liver transplant.

Survival curves based on NLR response after intervention are shown in Fig. 2. Those where the post-treatment NLR was normal had a much better prognosis than the groups that had elevated post-treatment NLR. In terms of 3-year OS, patients with initially normal NLR that rose after treatment had the worst OS at 44%. Patients with elevated NLR unresponsive to treatment had 47% 3-year OS. In contrast, patients whose NLR remained normal or normalized after treatment did significantly better with 3-year OS of 72% and 80%, respectively ($p < 0.01$). For patients treated with chemotherapy or Sorafenib, 24% had normal NLR that increased, and 7% had high NLR that decreased post-intervention. This was 15% and 6% for radiation therapy or RFA, 23% and 4% for Yttrium-90 or TACE, as well as 15% and 11% for hepatectomy or transplant. It should be noted that the number of patients in each treatment group is small and this should be interpreted with caution.

Discussion

We found that elevated NLR is an independent prognostic factor for worse OS and PFS. Moreover, sensitivity analysis shows that an elevated NLR is predictive of OS regardless of the specific cut-off point.

Of note, results from univariable analyses showed that NLR was associated with ethnicity and SES. Specifically, Hispanic and non-Hispanic black patients with HCC are more likely to have normal NLR compared to their non-Hispanic white and declined/unknown/other counterparts. This may be due to Hispanics presenting with earlier stage disease, as after controlling for stage the association was no longer significant. Patients with higher SES were also more likely to have elevated NLR compared to those with lower SES. Since non-Hispanic whites had more advanced disease and were in the highest SES category, it could contribute to the association between higher SES and elevated NLR. However, even after controlling for disease stage, the association is still present, albeit borderline significant at $p = 0.073$.

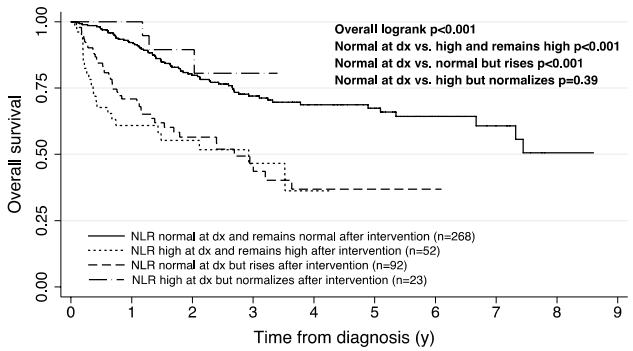

Fig. 2 Overall survival stratified by changes in NLR from before to after intervention

To our knowledge, there has only been one study looking at ethnic and socioeconomic differences in relation to NLR, which was performed in a healthy population. That study by Azab et al. [14] found that black and Hispanic participants had significantly lower mean NLR values, which is consistent with our results. However, it showed that SES is inversely associated with NLR in healthy participants, which is contrary to what we found in patients with HCC. While ethnic differences in inflammatory responses to HCC are easier to comprehend given likely differences in underlying genetic and social dispositions, the role of SES is unclear.

Interestingly, SES and ethnicity were not independent predictors of OS or PFS in our patient cohort. This result remains consistent with prior findings from our institution that ethnicity did not significantly impact OS [17]. Previous studies that found ethnic and SES differences in outcomes attributed the differences to less access to health care, more advanced cancer stage at diagnosis, as well as less curative treatment [13]. Though not focused on HCC, studies on other disease sites such as esophageal cancer showed that differences in OS by ethnicity and SES are no longer significant after controlling for covariates including treatment received [18]. For our cohort of HCC patients, we did not find differences in outcome based on SES, and the differences related to ethnicity did not persist when controlling for prognostic markers and treatment indication. The perceived differences in HCC outcome by ethnicity and SES may, therefore, be due to the difference in diagnosis and treatment, which is potentially modifiable.

With regards to NLR as a prognostic marker, the exact mechanism for how inflammation affects cancer development and progression has not been delineated, but different theories have been proposed. A high NLR reflects greater inflammatory response that could provide a favorable microenvironment for the tumor to invade and metastasize [3]. In addition, increased circulating neutrophils give rise to more circulating vascular endothelial growth factor (VEGF), which is a major contributor to tumor-related angiogenesis. Promotion of angiogenesis leads to increased likelihood of metastasis [19]. High NLR is also associated with the presence of tumor-associated

macrophages (TAMs), which secrete cytokines and cause neutrophilia [20]. Increased NLR can also be viewed as a relative lymphocytopenia, which would imply less robust lymphocyte-mediated anticancer immune response [21]. Lymphocytes are shown to inhibit invasion and metastasis of cancer cells by inducing cytotoxic cell death and through the production of cytokines. Therefore, NLR could serve as a composite score that reflects the status of the host immune system.

Our analysis indicates that NLR response post-treatment is a prognostic factor for survival regardless of treatment type. We found that patients with NLR that is either not responsive to treatment or becomes elevated after treatment, had much worse prognosis compared to patients whose NLR remained normal or normalized after treatment. Although there have been a few small-scale studies looking at TACE and RFA that showed an association with outcome [22], ours is the first large-cohort study to demonstrate that NLR change from before to after intervention is highly prognostic of OS, regardless of the fact that multiple different interventions were utilized. These results suggest that interventions that can lower the NLR score could lead to better disease outcome. Recently, anti-inflammatory therapy with canakinumab targeting the interleukin 1-B innate immunity pathway was shown to significantly decrease both the incidence and mortality of lung cancer [23]. Although medication targeting inflammation has not yet been tested in other cancers, further research in this direction is promising given the connection between inflammation and cancer development.

There are some notable limitations to our study. It is retrospective and reliant on medical record data with some patients having missing information. In addition, the heterogeneity of the patient cohort among the different treatments and the small number of patients in each specific treatment group precludes statistically valid conclusions to be drawn about the prognostic value of NLR in these subgroups. Another limitation is that there is no established clinically relevant cut-off for what is considered elevated NLR. In our study, we defined elevated NLR as > 4.0, although the independent prognostic value of NLR remained regardless of the specific cut-off used.

In conclusion, we demonstrated the prognostic importance of NLR in patients diagnosed with HCC with regards to OS and PFS. SES and ethnicity were not found to be independent predictors of disease outcome. Finally, the dynamic change in NLR from before to after treatment was an important prognostic factor for survival, and monitoring this routinely could provide a simple yet useful aid in clinical decision-making.

Compliance with ethical standards

Conflict of interest Yifei Zhang, N. Patrik Brodin, Nitin Ohri, Santiago Thibaud, Andreas Kaubisch, Milan Kinkhabwala, Madhur Garg, Chandan Guha and Rafi Kabarriti declare that they have no conflict of interest.

Ethical approval The study protocol has been approved by the institute's committee on human research.

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