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Prognostic significance of platelet-to-lymphocyte ratio in patients with hepatocellular carcinoma undergoing curative radiation therapy

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Purpose

- Growing evidences support that elevated platelet-to-lymphocyte ratio (PLR) is associated with poor clinical outcomes in human cancer and distant metastasis (DM) is the major contributor to the devastating prognosis.

- We aimed to investigate whether serum inflammatory parameters can help to predict the clinical outcomes in patients with unresectable hepatocellular carcinoma (HCC) undergoing curative radiation therapy (RT).

Materials and Methods

- **Study population**
- The inclusion criteria: a diagnosis of unresectable HCC by radiological or serological diagnostic criteria and receipt of RT with a potentially curative intent at doses of ≥30 Gy.
- The exclusion criteria: (a) receipt of RT with palliative intent at doses < 30 Gy, (b) lack of completion of the planned RT course, (c) loss to follow-up within 3 months after treatment, (d) lack of data for serum laboratory testing before, during, or after treatment, and (e) the presence of metastatic disease.
- Between January 2014 and April 2019, a total of 76 RT courses in 71 patients were eligible and analyzed in this study.

- **Definition of Serum Indices and Data Collection**
  LMR = lymphocyte count [10^9/L]/monocyte count [10^9/L]
  NLR = neutrophil count [10^9/L]/lymphocyte count [10^9/L]
  PLR = platelet count [10^9/L]/lymphocyte count [10^9/L]
  PNI = (5 × lymphocyte count [10^9/L]) + (10 × albumin [g/dL])
  SII = neutrophil count [10^9/L] × platelet count [10^9/L]/lymphocyte count [10^9/L]
  ALC = absolute lymphocyte count [10^9/L]
  A = 10 × albumin [g/dL]
  AAR = 10 × albumin [g/dL]/alkaline phosphatase [IU/L]
  P = 10 × total protein [g/dL]
  H = hemoglobin [g/dL]

Materials and Methods

- All serum indices obtained before, during, and after treatment were assessed to improve the accuracy of the study. For pretreatment indices, serum samples taken just before treatment (RT) were analyzed. For posttreatment indices, all serum indices during and after treatment (RT) were collected. We collected posttreatment data up to 3 months after the completion of treatment in consideration of the systemic posttreatment effects of RT.

• **Treatments**
- The combination treatment approach was applied in most of the study population.
  : Curative-aimed TACE or hepatic HAIC followed by RT
- Various methods for RT were used: 3-D CRT, Gating SBRT/IMRT, Arc therapy, sIMRT

• **Study End-points and Statistical analyses**
- Primary end-points: Distant control (DC) and overall survival (OS) rates
  Secondary study end points: Local control (LC) and intrahepatic control (IHC) rates
- To identify the optimal cutoff values for the study end points, the maximal chi-square test was applied using R statistics. The Kaplan–Meier method was used for survival analysis, and survival graphs were compared using the log-rank test. To assess the prognostic significance, the multivariate Cox proportional hazards model was used. A p-value < 0.05 was regarded as significant.

Results

- **Baseline patient and tumor characteristics**

Characteristics		N (%)
Age		
Mean±SD	61.4±10.6	
Gender		
	Male	62 (81.6)
	Female	14 (18.4)
ECOG PS		
	0	30 (39.5)
	1	43 (56.6)
	2	3 (3.9)
Comorbidity		
	No	36 (47.4)
	Yes	40 (52.6)
HCC etiology		
	Alcoholic	10 (13.2)
	HBV	43 (56.6)
	HCV	4 (5.3)
	NBNC	4 (5.3)
	Mixed	12 (15.8)
	Unknown	3 (3.9)

Combined PVT/IVT		
	No	44 (57.9)
	Yes	32 (42.1)
C-T-P score		
	5 (A)	37 (48.7)
	6 (A)	18 (23.7)
	7 (B)	12 (15.8)
	8 (B)	5 (6.6)
	9 (B)	3 (3.9)
	10 (C)	1 (1.3)
AFP (ng/mL)		
Mean±SD	709.5±1808.9	
PIVKA-II (mAU/mL)		
Mean±SD	3996.2±18160	

Results

- **Treatment characteristics**

Characteristics		N (%)
Pre-RT TACE/HAIC		
	No	2 (2.6)
	Yes	74 (97.4)
RT method		
	3-dimensional CRT	14 (18.4)
	Gating SBRT/IMRT	26 (34.2)
	Arc	25 (32.9)
	sIMRT	11 (14.5)
RT fraction number		
Median (range)	12 (4-30)	
RT fractional dose (Gy)		
Median (range)	5 (2-12)	
	≤ 5 Gy	53 (69.7)
	> 5 Gy	23 (30.3)

| Total BED₁₀ (Gy)		
Median (range)	72.6 (51.5-119)	
GTV sum (cc)		
Median (range)	55.3 (2.8-1288)	
Total liver volume (cc)		
Median (range)	1260.6 (551-2559.8)	
Mean total liver dose (cGy)		
Median (range)	2150.2 (327.5-4142.9)	
Mean liver dose (TL-PTV) (cGy)		
Median (range)	1615 (253.4-2993.9)	

Results

- **Numerical distribution of pre- and posttreatment serum indices**

Indices	Pre-SII	Pre-NLR	Pre-PLR	Pre-PNI	Pre-ALC	Pre-LMR	Pre-A	Pre-AAR	Pre-P	Pre-H
Mean±SD	374±347.8	2.6±1.6	119±69	41±8.1	1.3±0.7	2.8±1.1	35.3±5.2	0.1±0.05	71.3±9.3	12.7±1.8
Indices	Post-SII-H	Post-SII-L	Post-NLR-H	Post-NLR-L	Post-PLR-H	Post-PLR-L	Post-PNI-H	Post-PNI-L	Post-ALC-L	
Mean±SD	1251.4±1501.3	201.8±194.7	14.8±30.5	3.4±10.1	320±340	90.7±36.6	40.5±5.6	31.4±6.3	0.4±0.2	
Indices	Post-LMR-H	Post-LMR-L	Post-A-H	Post-A-L	Post-AAR-H	Post-AAR-L	Post-P-H	Post-P-L	Post-H-H	Post-H-L
Mean±SD	3.1±2.2	0.8±0.4	36.7±4.9	28.2±5.8	1±7.8	0.7±5.3	73.3±9.1	59.7±9.7	13.4±1.8	10.7±2.1

Results

- **Kaplan–Meier curves for DC and OS rates**
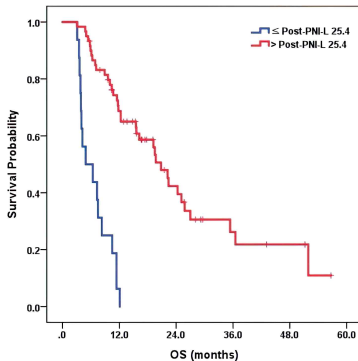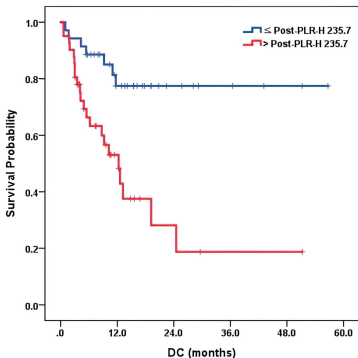
Results

- **Multivariate Cox proportional hazards analyses for major study end points**

End-points	Variables	P-value	Group	HR (95% CI)	1-year probability (%)
DC					
	Post-PLR-H	0.006	≤ 235.7	0.286 (0.117-0.700)	77.5
			> 235.7	1	53.1
	GTV sum	0.068	≤ 504.7	0.413 (0.160-1.067)	68.1
			> 504.7	1	28.6

OS					
	Post-SII-H	0.875	≤ 426.9	1	73
			> 426.9	1.076 (0.435-2.662)	47.2
	Post-PLR-H	0.096	≤ 235.7	0.552 (0.275-1.110)	72.9
			> 235.7	1	40.2
	Post-PNI-L	<0.001	≤ 25.4	4.790 (2.253-10.184)	0.63
			> 25.4	1	68.7
	Post-A-L	0.136	≤ 32	1.963 (0.809-4.759)	45.1
			> 32	1	80.7
	Post-H-L	0.735	≤ 12.3	1.188 (0.438-3.226)	45
			> 12.3	1	92.9
	Post-P-L	0.256	≤ 66	1.981 (0.609-6.444)	49.1
			> 66	1	79.4

Conclusions

- Serum-based indices independently predicted DC and OS rates in patients with unresectable HCC receiving curative RT.

- The highest posttreatment PLR ($\leq$235.7 vs. >235.7) and the lowest posttreatment PNI ($\leq$25.4 vs. >25.4) were significant prognostic factors for DC and OS rates, respectively.

- Appropriate selection of the most suitable cohorts and applicability of these parameters to HCC require further validation.