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Prognostic significance of prognostic nutritional index and hemoglobin to red cell distribution width ratio in metastatic colorectal cancer patients

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ABSTRACT

Aims: Malnutrition and systemic inflammation are poor prognostic factors in cancer. Prognostic nutritional index (PNI) and Hemoglobin to red blood cell distribution witdh (HRR) are considered indicators of malnutrition and systemic inflammation. We aimed to investigate the prognostic importance of PNI and HRR on metastatic colorectal cancer survival.

Methods: We retrospectively reviewed all patients diagnosed with metastatic colorectal cancer treated at Kayseri City Training and Research Hospital and Erciyes University Medical School. PNI is calculated as (serum albumin (g/L) +5 x total lymphocyte count (10^9/L)). And HRR was calculated as the ratio of hemoglobin (g/dl) and RDW (%). PNI was divided into two groups based on the cut off points 46.175 as PNI high and low. And we compared these two groups according to general characteristics and overall survival. We performed another comparision between HRR low and high groups based on the cut off points 0.8675 according to general characteristics and overall survival. Kaplan Meier method was used to analyse overall survival and compared survival rates with the log-rank test.

Results: We reviewed 346 metastatic colorectal cancer patients and we included 145 of them who fit to inclusion criteria to the study. Univariate analysis revealed that presence of initially metastatic disease, right located tumor, low HRR, low PNI were independent prognostic markers of poor overall survival. In multivariate analysis, presence of initially metastatic disease and low PNI remain statistically significant independent prognostic markers of poor survival. The median overall survival was statistically longer in HRR and PNI low groups than high groups.

Conclusion: Both PNI and HRR are associated with poor overall survival in metastatic colorectal cancer.

Keywords: Colon cancer, prognostic nutritional index, hemoglobin red cell distribution width ratio

INTRODUCTION

Colorectal cancer is the third most common cancer related death in the World.[1] Overall survival increased by adding biological agents in metastatic colorectal cancer last years.[2] Some molecular markers and clinical characteristics were associated with disease prognosis. Mutational status of KRAS/NRAS, BRAF, microsatellite instability status, tumor sideness were reported as some of the prognostic indicators.[3] Malnutrition and systemic inflammation are also poor prognostic factors in cancer.[4] The prognostic markers are still under investigation.

Prognostic nutritional index is calculated by the serum albumin and peripheral blood lymphocytes. Lymphopenia is related with inadequate cell mediated immune response and malnutrition.[5,6] Poor nutritional status and inflammation decrease production of albumin.[7] PNI is considered as an indicator of nutritional and systemic inflammatory status of cancer patients.[8] It has been studied as a prognostic marker in several cancers.[8-10] HRR is calculated by the hemoglobin and RDW. HRR is an another parameter that reflects nutritional status and systemic inflammation.[11] The knowledge of relationship between metastatic colorectal cancer survival and PNI and HRR is limited in literature. We hypothesized that these two malnutrition and systemic inflammation index could help us to predict prognosis and survival.

We aimed to investigate the prognostic importance of PNI and HRR on metastatic colorectal cancer survival.

METHODS

The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee

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(Date: 22.08.2023, Desicion No: 881). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We retrospectively reviewed all patients diagnosed with metastatic colorectal cancer treated at Kayseri City Training and Research Hospital and Erciyes University Medical School between January 2007 and May 2023 with follow up through is August 2023. The patients who had story of chronic disease like chronic cirrhosis and end stage renal disease, antibiotic use for active infection, chronic inflamattory diseases like systemic lupus eritemtaosis, blood transfusion in last 6 months and steroid use were excluded. We also excluded the patients whose laboratory test results were missing.

Patient characteristics, chemotherapy regimens, KRAS mutation status, tumor sideness, presence of lung or liver metastasis, number of metastatic sites, date of death, laboratory datas were examined from hospital patients' records and the patients files.

The counts of serum albumin, total lymphocyte, hemoglobin, RDW before initation of chemotherapy for metastatic disease were saved. PNI is calculated as (serum albumin (g/L) +5 x total lymphocyte count (10^9/L)). And HRR was calculated as the ratio of hemoglobin (g/dl) and RDW (%) before initiation of chemotherapy.

Hemoglobin (Hb) to RDW ratio was divided into two groups based on the cut off point 0.8675 as Hb to RDW high and low (area under the curve: 0.489 (0.395-0.584), sensitivity: 41.9% spesificity: 63.4%, p=0.825). The cut off value of HB to RDW were performed using ROC curve analysis. PNI was divided into two groups based on the cut off point 46.175 as PNI high and low (area under the curve: 0.705 (0.619-0.791), sensitivity: 79.7% spesificity: 56.3%, p<0.001). The cut off value of PNI were performed using ROC curve analysis.

Statistical Analysis

Median, min, max and frequencies were defined for the general characteristics. We performed chi-square and Fisher's exact test for comparision of categorical variables. Mann-Whitney U test were used for comparision of noncategorical variables. We used univariate and multivariate analysis with the use of cox regression analysis to determine association of some variables with overall survival. Kaplan Meier method was used to analyse overall survival and compared survival rates with the log-rank test. OS was defined from the date of chemotherapy initiation to the date of death or last visit. Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) software was used in all statistical analyses. A p value of <0.05 was considered statistically significant.

RESULTS

We reviewed 346 metastatic colorectal cancer patients and we included 145 of them who fit inclusion criteria to the study. The median age was 64 (26-87) years old. Sixty patients (41%) were female, 85 of them (59%) were male. Seventy one death were occured (49%). All of general characteristics were showed in **Table 1**.

Table 1. General characteristics

Variables	All patients	PNI low (n=55, 38%)	PNI high (n=90, 62%)	p	HRR low (n=88, 59%)	HRR high (n=57, 41%)	p
Age, year (min-max)	64(26-87)	63 (26-82)	65 (31-87)	0.744	63.5 (26-81)	63 (38-82	0.278
Age							
<65	75 (52)	31 (56)	44 (49)	0.398	42 (48)	33 (58)	0.240
≥65	70 (48)	24 (44)	46 (51)		46 (52)	24 (42)	
Gender							
Female	60 (41)	25 (45.5)	35 (39)	0.489	40 (45.5)	20 (35)	0.232
Male	85 (59)	30 (54.5)	55 (61)		48 (54.5)	37 (65)	
Initially metastatic							
Yes	118 (81)	43 (78)	75 (83)	0.511	77 (87.5)	41 (72)	0.028
No	27 (19)	12 (22)	15 (17)		11 (12.5)	16 (28)	
Tumor site							
Right	31 (21)	14 (25.5)	17 (19)	0.406	21 (24)	10 (17.5)	0.412
Left	114 (79)	41 (74.5)	73 (81)		67 (76)	47 (82.5)	
Liver metastasis							
Yes	99 (68)	35 (64)	64 (71)	0.364	61 (69)	38 (67)	0.855
No	46 (32)	20 (36)	26 (29)		27 (31)	19 (33)	
Lung metastasis							
Yes	54 (37)	18 (33)	36 (40)	0.479	26 (29.5)	28 (41)	0.022
No	91 (63)	37 (67)	54 (60)		62 (70.5)	29 (51)	
Number of metastasis							
1	89 (61)	33 (60)	56 (62)	0.861	56 (64)	33 (58)	0.492
≥2	56 (39)	22 (40)	34 (38)		32 (36)	24 (42)	
KRAS mutation							
Wild	94 (65)	34 (62)	60 (67)	0.334	54 (61)	40 (70)	0.371
Mutant	45 (31)	17 (31)	28 (31)		30 (34)	15 (26)	
Unknown	6 (4)	4 (7)	2 (2)		4 (5)	2 (4)	

PNI High and Low Groups

Fifty five of the patients (38%) were in PNI low group, 90 of them (62%) were in PNI high group. There were no statistically significant difference among the features. All of general characteristics were showed in **Table 1**.

HRR Low and High Groups

Eighty eight of the patients (59%) were in HRR low group, 57 of them (41%) were in HRR high group. The patients were heterogeneous according to initially metastatic disease and lung metastasis. Other variables were homogeneous in the group. All of general characteristics were showed in **Table 1**.

Univariate and Multivariate Analysis

Univariate analysis revealed that presence of initially metastatic disease 0.501(95% CI 0.300-0.836, p=0.008), right located tumor 0.567 (95 0.336-0.957, p=0.034, low HRR 0.591 (95% CI 0.358-0.974,p=0.039), low PNI 0.352 (95% CI 0.219-0.563,p=<001) were correlated with poor overall survival (**Table 2**).

We performed multivariate analysis with statistically significant parameters in univariate analysis. Presence of initially metastatic 0.362 (0.203-0.648, p=0.001) and low PNI 0.393 (0.242-0.637, p=<0.001) remain statistcally significant according to poor survival in multivariate analysis (**Table 2**).

Overall Survival

The median overall survival was 34 (14.69-53.30) months in HRR high group, 28 (23.29-32.70) months in HRR low group (p=0.035). The median overall survival was 44 (33.23-54.76) months in PNI high, 24 (15.14-32.85) months in PNI low group (P<0.001) (**Figure 1**).

DISCUSSION

Numerous studies have been established an association between systemic inflammation and poor cancer related survival.[9,12,13] Also poor nutritional status is related with poor survival.[14] PNI and HRR has been documanted as indicators of both systemic inflammation and nutritional status.[11] We demonstrated low PNI and HRR were independent indicators of poor survival.

Table 2. Univariate and multivariate analysis

Characteristics	Univariate analysis (Hazard ratio (CI 95%))	p	Multivariate analysis (Hazard ratio (CI 95%))	p
Age(<65 or ≥65)	0.937(0.580-.515)	0.791		
Gender (female or male)	1.463 (0.918-2.333)	0.110		
Initially metastatic (no or yes)	0.501 (0.300-0.836)	0.008	0.362 (0.203-0.648)	0.001
Tumor site (right or left)	0.567 (0.336-0.957)	0.034	0.625 (0.366-1.068)	0.086
Liver metastasis (no or yes)	0.737 (0.441-1.230)	0.243		
Lung metastasis (no or yes)	0.779 (0.480-1.263)	0.311		
Number of metastasis (1 or ≥2)	1.016 (0.627-1.647	0.948		
KRAS mutation (wild or mutant)	0.970 (0.573-1.642)	0.911		
HRR (low or high)	0.591 (0.358-0.974)	0.039	0.606 (0.340-1.080)	0.089
PNI (low or high)	0.352 (0.219-0.563)	<0.001	0.393 (0.242-0.637)	<0.001

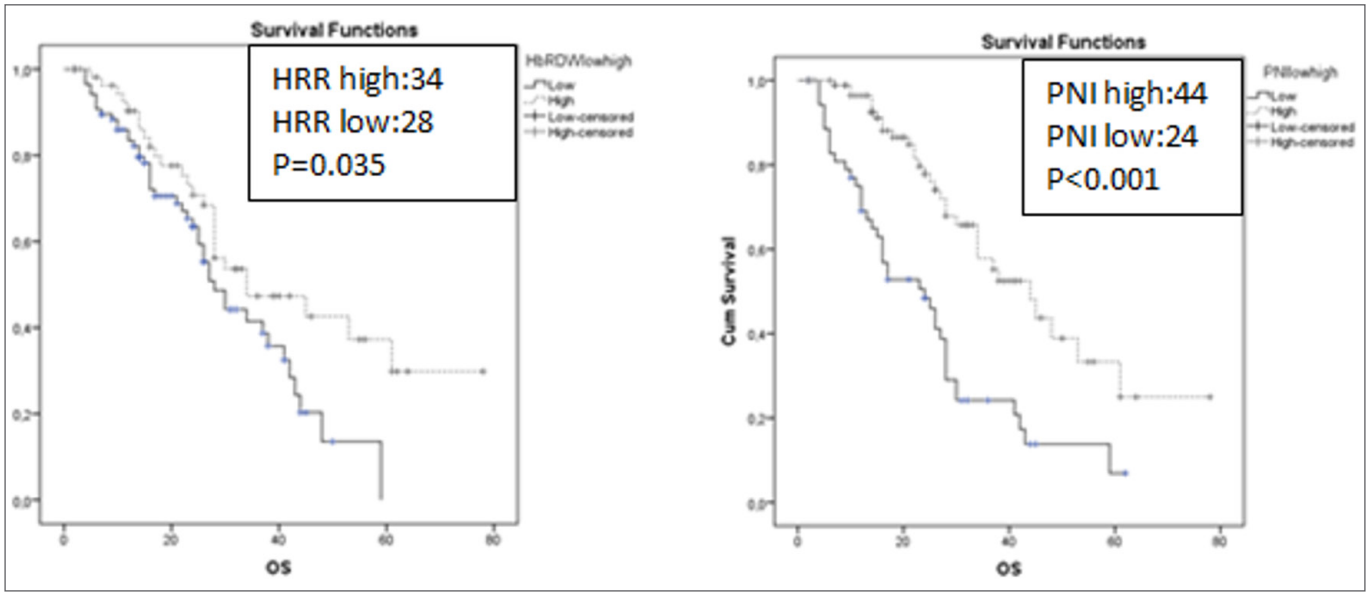

Figure 1. Comparision of overall survival in HRR and PNI low and high groups

PNI is calculated based on albumin and peripheral lymphocytes. Proinflammatory cytokins influence albumin production from hepatocytes.[15] Lymphophenia reflects immun and nutritional status.[16] Takamizawa et al.[17] reported that three nutritional and inflammtory prognostic index. One of them was PNI. They found the median overall survival was 33.8 months in PNI high group and 19.8 months in low PNI group. Our median overall survival was 34 months in PNI high group, 28 months in PNI low grup. In this study the survival difference were much more than ours among PNI low and high groups.[17] In this study right sided tumors were significantly more common in PNI high group. In our study left and right sided tumors were homogenous in both groups. Also in their study there was no knowledge of KRAS mutation. KRAS mutation both prognostic and predictive marker in colorectal cancer.[18] In our study distribution of PNI low and high groups according to KRAS mutation status is similar.

Tumor site is an another prognostic and predictive marker in colorectal cancer. It is suggested that overall survival is longer in left sided than right sided colon tumors.[19] In our study right sided tumor significantly predict poor overal survival in univariate analysis similarly to recent reports. However this prediction didn't remain significant after adjustment of other prognostic variables like prognostic nutritional index.

High levels of RDW is related so many conditions. Some of them were reduced erythropoietin levels due to proinflamatuar cytokins and oxidative stress.[20] These conditions are present in cancer patients. HRR is considered as a marker of poor overall survival.[21] Tuncel et al.[11] showed HRR was a significant predictor of overall survival in rectal cancer patients. They analyzed systemic inflammatory markers in univariate and multivariate analyzed. We found that the HRR was an independent predicor of poor overall survival. We differently added clinical and molecular prognostic characteristics to our multivariate analyse. After adjusted according to clinical characteristic HRR was not statistically significant predictor of overall survival in colorectal cancer.

We found that having initially metastatic disease were another independent prognostic marker. In our study 81% of the patients had initially metastatic disease. We didn't analysed adjuvant or neoadjuvant chemotheapy history in univarite and multivariate analysis. This finding should be researched with the other patients characteristics like adjuvant or neoadjuvant chemotherapy history and in large number of populations.

Our study had some limitations. Firstly retrospective design and small number of patients. Secondly the inclusion of less than half of the patients screened for the study.

CONCLUSION

Both PNI and HRR are associated with poor overall survival in metastatic colorectal cancer. We must also take into account these markers while treating metastatic colorectal patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 22.08.2023, Desicion No: 881).

Informed Consent: Because the study was designed retrospectively, no written informed consent from was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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