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Prognostic Value of Monocyte to High-Density Lipoprotein Cholesterol Ratio in Non-Muscle Invasive Bladder Cancer: Retrospective-Cohort Analyses

Kasa İnvaze Olmayan Mesane Kanserinde Monosit/Yüksek Yoğunluklu Lipoprotein Kolesterol Oranının Prognostik Değeri: Retrospektif Kohort Analizleri

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This study was presented as an oral presentation at the 33rd National Urology Congress, October 29-November 1, 2024, Antalya, Türkiye.

ABSTRACT Objective: The objective of this study was to examine the prognostic value of Monocyte to High-Density Lipoprotein cholesterol ratio (MHR), as measured prior to surgery, in patients with non-muscle-invasive bladder cancer (NMIBC) who underwent transurethral resection of the bladder tumour (TUR-B). **Material and Methods:** This retrospective analysis was conducted on data from patients who had undergone a TUR-B procedure for bladder cancer and whose pathology result was NMIBC pure urethelial cell carcinoma. Routine blood tests were performed within 30 days prior to TUR-B. Progression was defined as an increase in stage, indicating the advancement of the disease to the lamina propria [for example, from Ta to T1 or carcinoma in situ (CIS) to T1 or T1 plus CIS], or to muscle-invasive disease. The patients were divided into 2 groups according to their progression status. The mean MHR values and other clinicopathological features of the 2 groups were then compared. **Results:** The significant difference between the 2 groups was also found in the MHR. The median MHR was 1.8 in the progression group and 1.57 in the non-progression group. The receiver operating characteristic analysis yielded an optimal cut-off point for MHR of 1.72. At this value, the sensitivity was 81.6% and the specificity was 81.9%. While all parameters demonstrated a statistically significant impact on progression in both univariate and multivariate analyses, high MHR was identified as having a stronger effect than other parameters. The mean progression time was 55.5 months in patients with a low MHR value (<1.72) and 29.1 months in the high MHR group (>1.72). **Conclusion:** MHR can be incorporated into existing scoring systems as a cost-effective and readily quantifiable marker that can forecast advancement cancer in NMIBC patients.

Keywords: High-density lipoprotein; monocyte; non-muscle-invasive bladder cancer; progression

ÖZET Amaç: Bu çalışmanın amacı, mesane tümörünün transüretral rezeksiyonu (TUR-M) yapılan kas invaziv olmayan mesane kanserli [non-muscle-invasive bladder cancer (NMIBC)] hastalarda ameliyat öncesinde ölçülen Monosit/Yüksek Yoğunluklu Lipoprotein kolesterol oranının [Monocyte to High-Density Lipoprotein cholesterol ratio (MHR)] prognostik değerini incelemektir. **Gereç ve Yöntemler:** Bu retrospektif analiz, mesane kanseri nedeniyle TUR-M prosedürü uygulanan ve patoloji sonucu NMIBC saf üretelyal hücreli karsinom olan hastalardan elde edilen veriler üzerinde yapılmıştır. TUR-M'den önceki 30 gün içinde rutin kan testleri yapılmıştır. Progresyon, hastalığın lamina propriaya ilerlemesini [örneğin Ta'dan T1'e veya karsinoma in situdan carcinoma in situ (CIS) T1'e veya T1 artı CIS'e] veya kas invaziv hastalığa ilerlemesini gösteren evre artışı olarak tanımlanmıştır. Hastalar progresyon durumlarına göre 2 gruba ayrılmıştır. Daha sonra 2 grubun ortalama MHR değerleri ve diğer klinikopatolojik özellikleri karşılaştırılmıştır. **Bulgular:** İki grup arasındaki anlamlı fark MHR'de de bulundu. Ortanca MHR progresyon grubunda 1,8 iken progresyon olmayan grupta 1,57 idi. alıcı çalışma karakteristiği analizi, MHR için 1,72'lik bir optimal kesme noktası vermiştir. Bu değerde duyarlılık %81,6 ve özgüllük %81,9'dur. Tüm parametreler hem tek değişkenli hem de çok değişkenli analizlerde progresyon üzerinde istatistiksel olarak anlamlı bir etki gösterirken, yüksek MHR'nin diğer parametrelerden daha güçlü bir etkiye sahip olduğu belirlenmiştir. Ortalama progresyon süresi düşük MHR değerine (<1,72) sahip hastalarda 55,5 ay, yüksek MHR grubunda (>1,72) ise 29,1 ay olmuştur. **Sonuç:** MHR, NMIBC hastalarında kanserin ilerlemesini öngörebilen uygun maliyetli ve kolayca ölçülebilir bir belirteç olarak mevcut skorlama sistemlerine dâhil edilebilir.

Anahtar Kelimeler: Yüksek yoğunluklu lipoprotein; monosit; kas invaziv olmayan mesane kanseri; progresyon

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Bladder cancer (BC) is the 4th most commonly diagnosed cancer in men in the US and the 8th leading cause of cancer death.[1] At the initial presentation, approximately 75% to 80% of patients present with non-muscle-invasive bladder cancer (NMIBC), including Ta tumours confined to the mucosa, T1 tumours with submucosal invasion, and carcinoma in situ (CIS) with flat and high-grade dysplastic lesions.[2] The standard treatment for bladder tumours is transurethral resection of the bladder tumour (TUR-B) combined with intravesical therapy, which is typically recommended in cases where the risk of disease recurrence and progression is high.[3]

The management of NMIBC in stage pT1 represents a significant challenge for urologists. It is estimated that 1/3 of patients with pT1G3 tumours will progress to muscle invasive bladder cancer (MIBC) and require radical cystectomy.[4] Furthermore, these patients are known to benefit from early cystectomy. However, it is likely that a significant proportion of patients will undergo this procedure unnecessarily, given the high morbidity and mortality rates associated with cystectomy.[5] Conversely, patients with MIBC who experience disease progression from primary NMIBC have a less favorable prognosis than those presenting with primary MIBC. Despite radical cystectomy, up to 50% of these patients succumb to their disease.[6] Enhancing the precision of recurrence and progression prediction can facilitate the formulation of follow-up strategies for individuals at elevated risk, provide guidance on the timing of radical cystectomy, and identify those most likely to derive benefit from novel therapeutic agents under investigation in clinical trials.[7]

The recurrence and progression rates for individual patients can be predicted using the scoring models developed by the European Organization for Research and Treatment of Cancer (EORTC) or the Spanish Urological Club for Oncological Therapy (CUETO).[8,9] These models for predicting recurrence and progression utilize clinicopathological characteristics, including T-stage, tumour grade, focality, size, involvement of the prostatic urethra and the presence of concomitant CIS or lymphovascular invasion (LVI).[10] However, the utility of these prognostic factors in predicting patient outcomes after treatment is limited.[11] It is therefore evident that more objective parameters are required to assist the clinician in making an informed decision.

An increasing body of evidence substantiates the involvement of inflammatory markers in the aetiology of urothelial cancers. A number of biomarkers derived from routine blood tests, including hemoglobin levels, platelet counts, leukocyte counts and C-reactive protein, have been subjected to evaluation in recent years with a view to predicting BC outcomes.[12] Monocytes (Ms) are released into the circulation from their precursors in the bone marrow and migrate into tissues, releasing proinflammatory cytokines at sites of inflammation. This process influences the severity of inflammation, which is considered an inflammatory biomarker. Moreover, high density lipoprotein cholesterol (HDL-C) has antioxidant properties that safeguard endothelial function. It may therefore be posited that the M count-to-high-density lipoprotein cholesterol (HDL-C) ratio (MHR) may serve as a reflection of inflammatory status and may be associated with the development of chronic inflammatory diseases.[13] A review of the literature reveals the existence of several publications that assess the predictive value of the MHR ratio and its correlation with clinicopathological features in colorectal, hepatocellular, and thyroid cancers.[14-16]

The objective of this study was to examine the prognostic value of MHR, as measured prior to surgery, in patients with non NMIBC who underwent TUR-B.

MATERIAL AND METHODS

The study included patients treated at our institution between January 2010 and September 2018. Following institutional review board approval, a retrospective analysis was performed on data from patients who had undergone TUR-B for BC and whose pathology result was NMIBC (high grade Ta and T1) pure urothelial cell carcinoma. All surgical procedures were conducted by highly experienced urologists within our department. Following the initial resection, the surgeon recorded the location, size, and number of tumours on a bladder map. As all patients in the study had high-grade tumours, a second TUR was performed within the initial 6 weeks following

the primary procedure, in accordance with recommendations from the European Association of Urology (EAU).[3] Routine blood tests were performed within 30 days prior to TUR-B. Patients with active autoimmune disease, chronic inflammatory disease or hematological disease, and a history of concomitant secondary cancer were excluded from the study, as were patients who did not receive intravesical Bacillus Calmette-Guérin (BCG) or did not complete the courses. Patients with variant histology were also excluded. The MHR was calculated as the ratio of Ms to HDL-C and the MHR ratio was multiplied by 100 for ease of interpretation.

Given that all patients in the study had high-grade tumours, the recommendation of the EAU was followed and intravesical BCG immunotherapy was administered as induction and maintenance treatment to each patient.[3] In general, patients were monitored using cystoscopy and urinary cytology at 3-monthly intervals for the 1st 2 years, and at 6-monthly intervals thereafter up to 5 years in the absence of any tumour recurrence or progression. The time to progression was analysed in relation to the initial TUR-B. Progression-free survival (PFS) was defined as the time from the date of initial TURB (before BCG induction) to the date of detection of progression. Progression was defined as an increase in stage, indicating the advancement of the disease to the lamina propria (for example, from Ta to T1 or CIS to T1 or T1 plus CIS), or to muscle-invasive disease (stage T2).[12]

The patients were divided into 2 groups according to their progression status. The mean MHR values and other clinicopathological features of the 2 groups were then compared.

STATISTICAL ANALYSES

The analyzes were made via IBM SPSS statistics 27.0. To examine numeric variables' normality, we used the Shapiro-Wilk test. The numerical variables with a normal distribution were expressed as mean±standard deviation. Data without a normal distribution were presented as median (minimum-maximum). Categorical variables were presented as number and percent. The Mann-Whitney U test was employed for the purpose of statistical analysis. The chi-squared test was employed to ascertain the negative and positive predictive values and to investigate the impact of discrepancies in parameters on progression. A receiver operating characteristic (ROC) analysis was employed to ascertain the predictive values of MHR cut-off values for progression. Kaplan-Meier analysis was employed to calculate overall survival curves for patients who exhibited progression and those who did not, and the resulting curves were compared using the log-rank test. A Cox regression analysis was conducted to determine which values were significantly associated with progression. A p value of less than 0.05 was considered to be statistically significant.

ETHICS APPROVAL

It was determined that the study complied with the Declaration of Helsinki, legal regulations, good clinical practices and ethical principles, and was approved by the Prof. Dr. Cemil Taşçıoğlu City Hospital Non-Interventional Research Ethics Committee with the decision dated 27.05.2024 and numbered 2024-114. Written informed consent was obtained from all participants.

RESULTS

A total of 450 patients were enrolled in the study. The demographic profile of the progression group revealed that 123 individuals (34.2%) were male and 29 (32.2%) were female. Nevertheless, the impact of gender on progression was not statistically significant (p: 0.727) (Table 1).

Of the patients, 315 (70%) were classified as having a high-grade Ta, while 135 (30%) were identified as having a high-grade T1. Progression was observed in 152 patients (33.7%), of whom 92 were in the Ta stage and 60 were in the T1 stage. A statistically significant correlation was identified between T stage and progression (p=0.002) (Table 1).

The analysis revealed that tumour size, the presence of LVI and CIS were significantly associated with progression (p=0.001, 0.001 and 0.001, respectively) (Table 1).

The significant difference between the 2 groups was also found in the MHR. The median MHR was 1.8 in the progression group and 1.57 in the non-pro-

TABLE 1: Progresyon gruplarına göre hastaların karakteristik özellikleri

		Progression		
	Parameters	**Yes**	**No**	**p value**
	Monocyte (103/µL)	0.6 (0.3-0.9)	0.5 (0.3-0.9)	**0.001**[a*]
	HDL (mg/dL)	33.5 (11-52)	34 (11-52)	0.217[a]
	MHR	1,8 (1.4-2.7)	1.57 (0.7-2.7)	**0.001**[a*]
	Age (year)	56 (40-70)	55 (40-70)	0.586[a]
	Size (cm)	4 (1-6)	3 (1-5)	**0.001**[a*]
Gender (n, %)	Male	123 (34.2)	237 (65.8)	0.727[b]
	Female	29 (32.2)	61 (67.8)	
Smoke (n, %)	Yes	114 (44.9)	140 (55.1)	**0.001**[b*]
	No	38 (19.4)	158 (80.6)	
Size (n, %)	<3cm	48 (23)	161 (77)	**0.001**[b*]
	>3cm	104 (43.2)	137 (56.8)	
Stage (n, %)	Ta	92 (29.2)	223 (70.8)	**0.002**[b*]
	T1	60 (44.4)	75 (55.6)	
LVI (n, %)	(+)	77 (42.8)	103 (57.2)	**0.001**[b*]
	(-)	75 (27.8)	195 (72.2)	
CIS (n, %)	(+)	30 (56.6)	23 (43.4)	**0.001**[b*]
	(-)	122 (30.7)	275 (69.3)	
MHR (n, %)	≥1.72	124 (69.7)	54 (30.3)	**0.001**[b*]
	<1.72	28 (10.3)	244 (89.7)	

[a]Mann-Whitney U test; [b]Chi-square test; *significant. HDL: High density lipoprotein; MHR: Monocyte to high-density lipoprotein cholesterol ratio; LVI: Lymphovascular invasion; CIS: Carcinoma in situ.

gression group (p=0.001) (Table 1). ROC analysis was conducted to ascertain the MHR cut of that could predict disease progression. The area under the curve was 0.889 [95% confidence interval (CI) 0.858-0.919], and the curve was statistically significant (p=0.001). The ROC analysis yielded an optimal cut-off point for MHR of 1.72. At this value, the sensitivity was 81.6% and the specificity was 81.9% (Figure 1). Progression was observed in 124 patients with a high MHR (>1.72), whereas no progression was observed in 244 patients with a low MHR (<1.72). The positive predictive value and negative predictive value of MHR in predicting progression were found to be 69.7% and 89.7%, respectively, according to the results (Table 1).

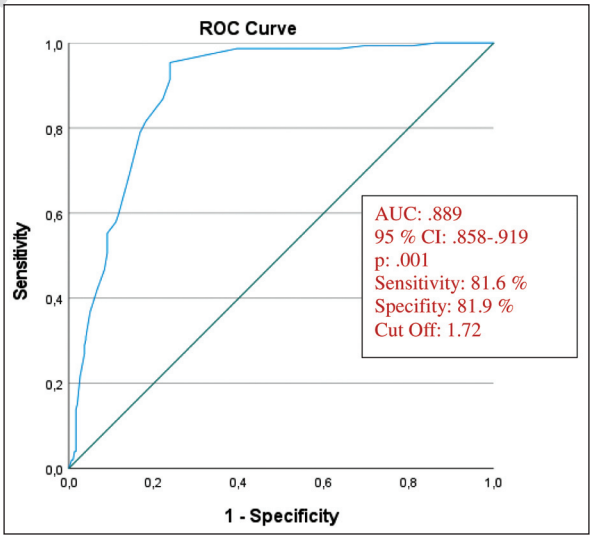

FIGURE 1: Determination cut off value for predicting progression by the ROC analyses
ROC: Receiver operating characteristic

A Cox regression analysis was conducted to ascertain the impact of multiple histological parameters, including MHR, the presence of CIS and LVI, tumour size, and stage, on disease progression. The analysis revealed statistically significant differences between the groups. While all parameters demonstrated a statistically significant impact on progression in both univariate and multivariate analyses, high MHR was identified as having a stronger effect than other parameters [p=0.001, Exp (B) = 8.16, CI (5.304-12.555)] (Table 2).

TABLE 2: Results of the Cox regression analyses

	Progression									
	Univariate					Multivariate				
				95% CI for Exp (B)					95% CI for Exp (B)	
	B	p value	Exp (B)	Lower	Upper	B	p value	Exp (B)	Lower	Upper
Tumor size[a]	0.869	**0.001***	2.385	1.671	3.405	0.394	**0.033***	1.483	1.031	2.132
Tumor stage[b]	0.553	**0.001***	1.739	1.256	2.408	0.491	**0.007***	1.634	1.147	2.328
Smoke[c]	1.018	**0.001***	2.768	1.917	3.997	0.538	**0.007***	1.712	1.159	2.529
LVI[d]	0.584	**0.001***	1.794	1.305	2.466	0.351	**0.043***	1.420	1.010	1.995
CIS[e]	0.928	**0.001***	2.530	1.695	3.774	0.594	**0.004***	1.812	1.205	2.724
MHR[f]	2.343	**0.001***	10.411	6.891	15.728	2.099	**0.001***	**8.160**	5.304	12.555

[a]ref <3cm; [b]ref: Ta; [c]ref: no smoking; [d]ref: LVI:+; [e]ref: CIS (-); [f]ref MHR <1.72; *significant. CI: Confidence interval; LVI: Lymphovascular invasion; CIS: Carcinoma in situ; MHR: Monocyte to high-density lipoprotein cholesterol ratio.

Finally, the PFS was calculated using the Kaplan-Meier analysis method. The results of the analysis indicated that the mean progression time was 55.5 months in patients with a low MHR value (<1.71) and 29.1 months in the high MHR group (>1.71) (Table 3 and Figure 2). The observed difference was statistically significant (p=0.001).

TABLE 3: Progression free survival according to MHR cut-off groups

			95% CI		
	Month	Std Error	Lower	Upper	p value
MHR<1.71	55.565	0.797	54.004	57.127	0.001*
MHR>1.71	29.157	1.555	26.109	32.206	
Overall	45.092	0.992	43.149	47.036	

*Log Rank test, significant. MHR: Monocyte to high-density lipoprotein cholesterol ratio; CI: Confidence interval.

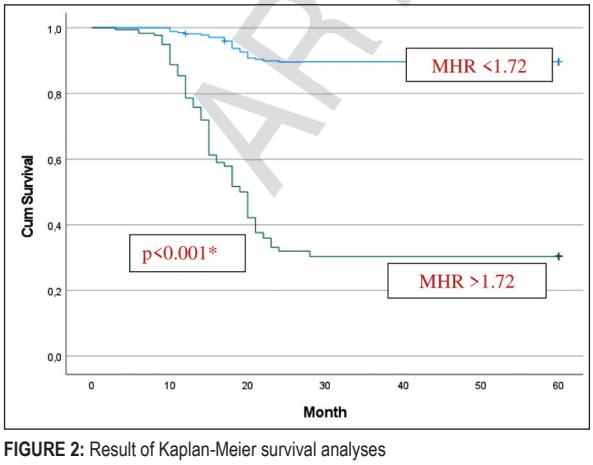

FIGURE 2: Result of Kaplan-Meier survival analyses
*Log rank test

DISCUSSION

The objective of our study was to examine the predictive capacity of MHR in patients with NMIBC. It is noteworthy that our analysis revealed several significant findings. Our findings indicate that MHR is a predictor of disease progression in this patient population.

The tumour microenvironment is typified by the stimulation of the immune system, which results in an increase in various host components, including stromal cells, growing blood vessels and inflammatory infiltrates.[17] All of these components play a significant role in the development and progression of numerous malignancies, including BC, through the release of cytokines by the tumour microenvironment.[18] A review of the literature reveals that various systemic inflammatory markers have been evaluated, with encouraging results.

Akan et al. investigate the potential predictive role of the systemic immune-inflammation index (SII) on BCG response in patients with high-risk NMIBC. Their findings suggest that the SII may be a promising biomarker for predicting BCG failure in patients with high-risk NMIBC. The findings indicated that a tumour exceeding 30 mm in diameter and a high SII concurrently elevated the likelihood of progression by a factor of 3.6.[19] In another study, D'Andrea et al. conducted an evaluation of the prognostic role of the neutrophil-to-lymphocyte ratio (NLR) in patients with primary NMIBC. In both univariate and multivariate analyses, a high NLR was found to be

significantly associated with PFS. In this retrospective study comprising 918 patients, the authors proposed the incorporation of NLR into a predictive model for the prediction of RFS and PFS in patients with NMIBC.[7] In a retrospective study of 3 systemic inflammatory markers NLR, platelet-to-lymphocyte ratio, and lymphocyte-to-M ratio, Cantiello et al. demonstrated that the combination of these markers in a predictive multivariable model can effectively predict the risk of disease recurrence and progression in patients with high-risk NMIBC.[12]

The prognostic predictive effect of MHR has been investigated in a number of cancer types other than urological cancers. Zhang and colleagues identified MHR, in conjunction with Cancer Antigen19-9 and carcinoembryonic antigen, as a potentially valuable predictor of colorectal cancer progression.[15] In a recent study, Miao et al. examined the correlation between the MHR and the prognosis of patients with metabolically associated fatty liver disease-related hepatocellular carcinoma. The authors proposed that MHR may serve as a potential predictor of prognosis in these patients.[16]

The present study represents a pioneering investigation into the prognostic impact of MHR in urological cancer. Our findings indicate that patients with high-grade Ta and T1 stage NMIBC and high MHR scores exhibit worse oncological outcomes with respect to progression. Therefore, elevated MHR values may assist in the identification of patients who may potentially benefit from radical cystectomy as a curative intervention.

It should be noted that our study is not without limitations, for a number of reasons. Single-centre study, small number of patients and retrospective nature are the limitations of our study. The fact that our study was single centre, our hospital is not a cancer centre may have contributed to the low number of patients. Due to the retrospective nature of this study, there may be selection bias; therefore, conclusions should be drawn with caution when evaluating the results. Despite these limitations, the results do not contradict the existing literature describing the relationship between inflammation and cancer.

CONCLUSION

MHR can be incorporated into existing scoring systems as a cost-effective and readily quantifiable marker that can forecast advancement in NMIBC patients. Further prospective studies with a larger number of patients are required.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Levent Özcan, Veysel Sezgin;* ***Design:*** *Ahmet Boylu, Musab Ümeyir Karakanlı;* ***Control/Supervision:*** *Alper Ötunçtemur, Emre Can Polat;* ***Data Collection and/or Processing:*** *Veysel Sezgin, Musab Ümeyir Karakanlı;* ***Analysis and/or Interpretation:*** *Mehmet Gökhan Culha, Mustafa Erkoç;* ***Literature Review:*** *Eyyüp Danış, Muammer Bozkurt;* ***Writing the Article:*** *Levent Özcan;* ***Critical Review:*** *Levent Özcan;* ***References and Fundings:*** *Emre Can Polat.*

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