Research Article

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Is the CONUT score a prognostic index in multiple myeloma?

CONUT skoru multipl myelomda prognostik bir gösterge midir?

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Abstract

Purpose: We aimed to evaluate the impact of the Controlling Nutritional Status (CONUT) score on prognosis in patients with multiple myeloma (MM).

Materials and methods: Our study was designed retrospectively. We calculated the CONUT score based on serum albumin, total cholesterol and lymphocytes. The study included 213 patients; 99 (46.5%) were female and 114 (53.5%) were male. The median follow-up period was 38 months (1-161).

Results: The median age was 64 years. We participated the patients into four groups. It was defined as CONUT scores: normal (0-1), low (2-4), moderate (5-8), and high (9-12). We found significant differences between overall survival (OS) and progression-free survival (PFS) with regard to CONUT score, respectively, as high (OS:12, PFS:1 months), moderate (OS:27, PFS:13 months) and low (OS:54, PFS:28 months) (p<0.001 and p=0.001). In the multivariate analysis for OS, having moderate CONUT score (HR: 2.21, p=0.005) and high CONUT score (HR: 2.38, p=0.033) were increased the risk of mortality. In the multivariate analysis for PFS, compared to a normal CONUT score, a moderate CONUT score (HR: 1.85, p=0.007), and a high CONUT score (HR: 2.01, p=0.043) were found to increase the risk of progression.

Conclusion: We found that a high CONUT score is related to decreased OS and PFS. In our study, we showed that the CONUT score is an independent, useful and strong prognostic index in MM.

Keywords: CONUT score, multiple myeloma, survival, prognosis.

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Öz

Amaç: Multiple Myelom (MM) hastalarında CONUT skorunun prognoza etkisini değerlendirmeyi amaçladık.

Gereç ve yöntem: Çalışmamız retrospektif bir çalışma olarak tasarlandı. CONUT skorunu serum albumin, total kolesterol ve lenfosit değerlerine göre hesapladık. Bu çalışmaya 99'u (%46,5) kadın, 114'ü (%53,5) erkek olmak üzere 213 hasta dahil edildi. Median takip süresi 38 ay idi (1-161).

Bulgular: Median yaş 64 idi. Hastaları CONUT skoruna göre dört gruba ayırdık: normal (0-1), düşük (2-4), orta (5-8) ve yüksek (9-12). CONUT skoruna göre genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) arasında sırasıyla yüksek (OS:12, PFS:1 ay), orta (OS:27, PFS:13 ay) ve düşük (OS:54, PFS:28 ay) anlamlı farklar bulduk (p<0,001 ve p=0,001). OS için yapılan çok değişkenli analizde CONUT skorunun orta düzeyde olması 2,21 kat (HR:2,21, p=0,005), CONUT skorunun yüksek olması 2,38 kat (HR:2,38, p=0,033) mortalite riskini arttırıyordu. PFS için yapılan çok değişkenli analizde normal CONUT düzeyiyle karşılaştırıldığında orta derecede CONUT skorunun (HR:1,85, p=0,007), yüksek CONUT skorunun (HR:2,01, p=0,043) ilerleme riskini arttırdığı belirlendi.

Sonuç: Yüksek CONUT skorunun OS ve PFS'de azalma ile ilişkili olduğunu belirledik. Çalışmamızda CONUT skorunun MM'da bağımsız, güçlü bir prognostik indeks olduğunu gösterdik.

Anahtar kelimeler: CONUT skor, multipl myelom, sağkalım, prognoz.

Coşkun EN, Akgün Çağlıyan G. CONUT skoru multipl myelomda prognostik bir gösterge midir? Pam Tıp Derg 2025;18:628-636.

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Introduction

Multiple myeloma (MM) is a disease caused by the uncontrolled proliferation of plasma cells that secrete monoclonal antibodies [1]. Multiple myeloma is a disorder that accounts for 1% of cancers and 10% of hematologic malignancies [2]. The incidence of MM is increased with age; it is more common in men [3]. Over the years, numerous staging systems have been developed to estimate prognosis in MM. Although the International Staging System (ISS) is the most widely accepted, it has been updated to the Revised ISS (R-ISS) to include lactate dehydrogenase (LDH) levels and cytogenetic characteristics. According to R-ISS, a stage is defined as stage I, II and III. When the stage increases, OS and PFS will decrease. R-ISS is a system that is more predictive of treatment in newly diagnosed transplant-eligible myeloma patients, but it only works with short-term studies that include patients under 65 years of age. For this reason, there are geriatric system-based care needs such as age, performance status and comorbidities. MM is a plasma cell dyscrasia with clinical findings and features of multiple organ involvement. Firstly, patients with MM apply to non-hematological medical departments such as nephrology, physical therapy, and neurosurgery. Pathological fractures due to osteolytic lesions are the most common symptoms. Particularly painful vertebral fractures and radicular back and waist pain are caused. Other clinical findings include anemia, infections, osteolytic lesions, neuropathy and renal involvement. Pneumonia, urinary system diseases and sepsis can be observed. Renal involvement is related to hyperuricemia, hypercalcemia, infections and tubulopathy. Fatigue, constipation, nausea and confusion are clinical findings due to hypercalcemia. Due to hyperviscosity syndrome, thrombosis and bleeding are rare. However, it is an important clinical condition needing plasmapheresis. Systemic therapy is usually inevitable at the time of diagnosis of MM. The decision of ASCT is still the most important parameter in therapy of MM. Initial therapy should be determined according to patients' eligibility for ASCT. Patients who are eligible for ASCT are <65-70 years old, have few comorbidities and fit. Despite the emergence of new-generation therapeutic agents, MM remains an incurable malignancy [4-6].

Malnutrition has occured as a widespread problem in patients with cancer. It has been attempted to be defined by components such as inadequate nutrition, weight loss, immobility, and sarcopenia. A more objective method is Controlling Nutritional Status (CONUT score), which is calculated according to serum albumin, total cholesterol levels and lymphocyte values. It has recently gained much attention and provides valuable insights into the immuno-nutritional status [7, 8]. The CONUT score has been demonstrated in various cancer types and in cardiovascular diseases by correlating nutritional and immune status with disease severity and adverse clinical outcomes [8-11]. Thus, elucidating the effect of the CONUT score in hematological malignancies has gained impetus in recent years. In our study, we examined the prognostic significance of the CONUT score in patients diagnosed with MM.

Materials and methods

Patients

The study included 213 patients newly diagnosed with MM who presented to the hematology clinic between 2008 and 2023. It was a retrospective cross-sectional study. The study protocol was approved by the Pamukkale University Faculty of Medicine Ethics Committee (date: 05.09.2023, issue: 60116787-020-415620). Due to the retrospective design, no interventions or procedures were performed on the patients. Patients with unavailable clinical or laboratory data at diagnosis and those receiving lipid-lowering therapy were excluded. Data collected at diagnosis included immunoglobulin subtypes, R-ISS stages, CONUT score, OS, and PFS. The R-ISS was evaluated based on ISS and cytogenetic characteristics.

The patients had received chemotherapy as bortezomib, thalidomide, lenalidomide, daratumumab, carfilzomib, ixazomib, and pomalidomide. The first therapy was bortezomib ± cyclophosphamide and steroid due to the payment order in our country. Patients were categorized based on ASCT status as having undergone one, two, or no transplants. Some patients received immunomodulatory, proteasome inhibitor, and monoclonal antibody treatments at an earlier stage, which was related to availability and drug payment instructions at

different periods in our country. Some patients had received treatments earlier with off-label approval.

CONUT score

The CONUT score is a method that provides insight into the nutritional status and is calculated with points as follows: Serum albumin: ≥3.5 g/dL, 3.0-3.49 g/dL, 2.5-2.99 g/dL, <2.5 g/dL (0, 2, 4 ,6 points). Lymphocyte count: ≥1600/mm^3, 1200-1599/mm^3, 800-1199/mm^3, <800/mm^3 (0, 1, 2, 3 points). Total cholesterol: ≥180 mg/dL, 140-179 mg/dL, 100-139 mg/dL, <100 mg/dL (0, 1, 2, 3 points) respectively. The sum of the scores categorizes nutritional status as follows: Score 0-1: Normal; 2-4: Low; 5-8: Moderate; and 9-12: High malnutrition.

Statistical analysis

We analyzed data using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). We presented descriptive statistics as counts and percentages for categorical variables and as means and medians (with minimum and maximum). We defined OS as the time from diagnosis to the last follow-up or death. We defined PFS as the time from diagnosis to the last follow-up, disease progression, relapse, or death. We conducted comparisons of OS and PFS using the Kaplan-Meier method. Finally, we performed multivariate Cox regression analyses to evaluate the influence of various clinical variables on mortality and progression risk. We considered a *p*-value of <0.05 statistically significant.

Results

Patient characteristics

We analyzed 213 patients with MM, comprising 114 men (53.5%) and 99 women (46.5%). The median age was 64 years (min: 40-max: 89). According to the R-ISS, 29 (13.6%) were classified as Stage I, 58 (27.2%) as Stage II, and 126 (59.2%) as Stage III in all patients. In terms of immunoglobulin subtypes, 76 patients (35.7%) had immunoglobulin (Ig) G kappa, 49 patients (23.0%) had Ig G lambda, 17 patients (8.0%) had Ig A kappa, 19 patients (8.9%) had Ig A lambda, 31 patients (14.6%) had kappa light chain, and 21 patients (9.9%) had lambda light chain. Renal dysfunction was present in 131 patients (61.5%). Regarding autologous stem cell transplantation (ASCT), 90 patients (42.3%) did not undergo ASCT, 110 patients (51.6%) underwent one ASCT, and 13 patients (6.1%) underwent ASCT twice. Based on the CONUT score, 55 (25.8%) had a normal score, 91 (42.7%) had a low score, 54 (25.4%) had a moderate score, and 13 patients (6.1%) had a high score. The median follow-up duration was 38.0 months (1-161). The median OS was 50 months (5-year OS, 41.6%; 95% CI, 40.38%-59.61%) (Figure 1a and 1b). The median PFS was 22 months (5-year PFS, 18.6%; 95% CI, 17.17%-26.82%) (Figure 2a and 2b). Demographic characteristics and laboratory data, OS and PFS are summarized in Tables 1a-1d.

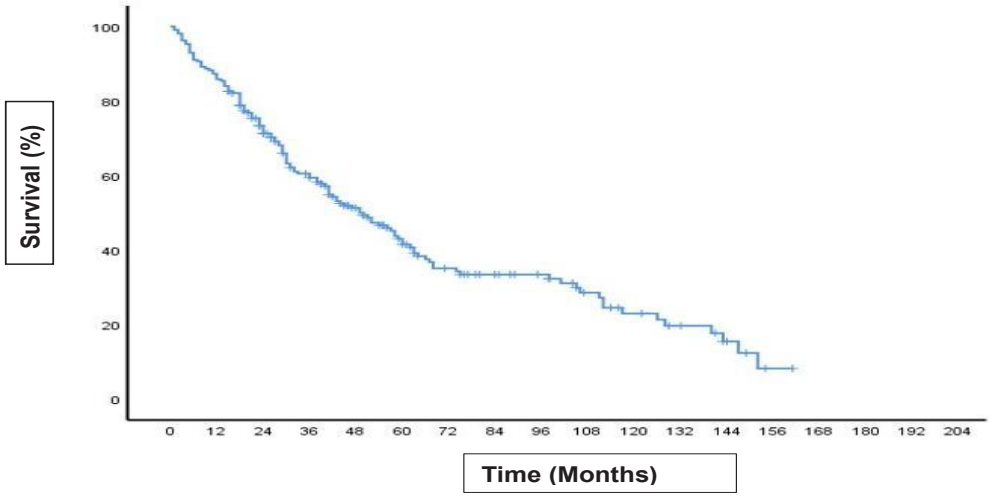

Figure 1a. Survival (%); Time (months)

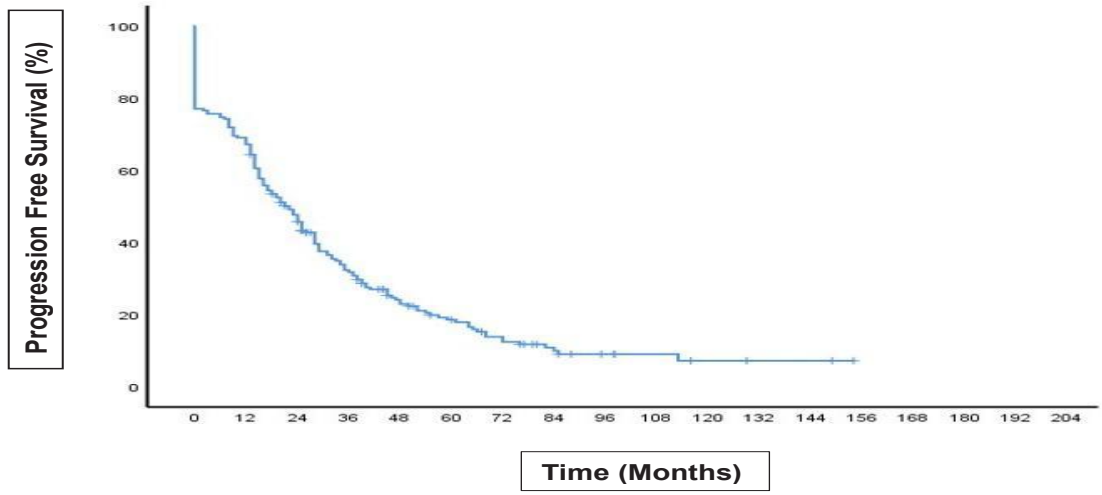

Figure 1b. PFS (%); Time (months)

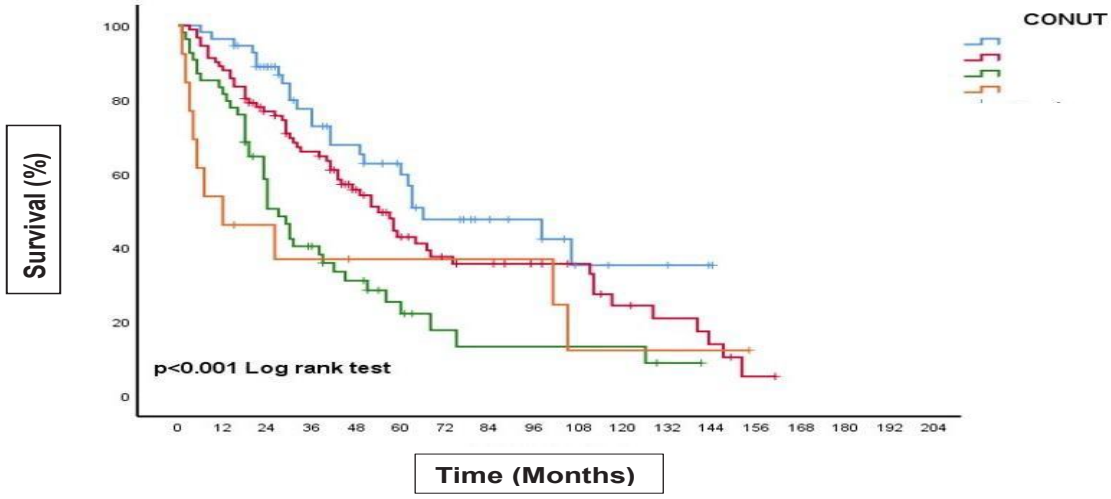

Figure 2a. Survival (%); Time (months); CONUT (normal, low, moderate, high)

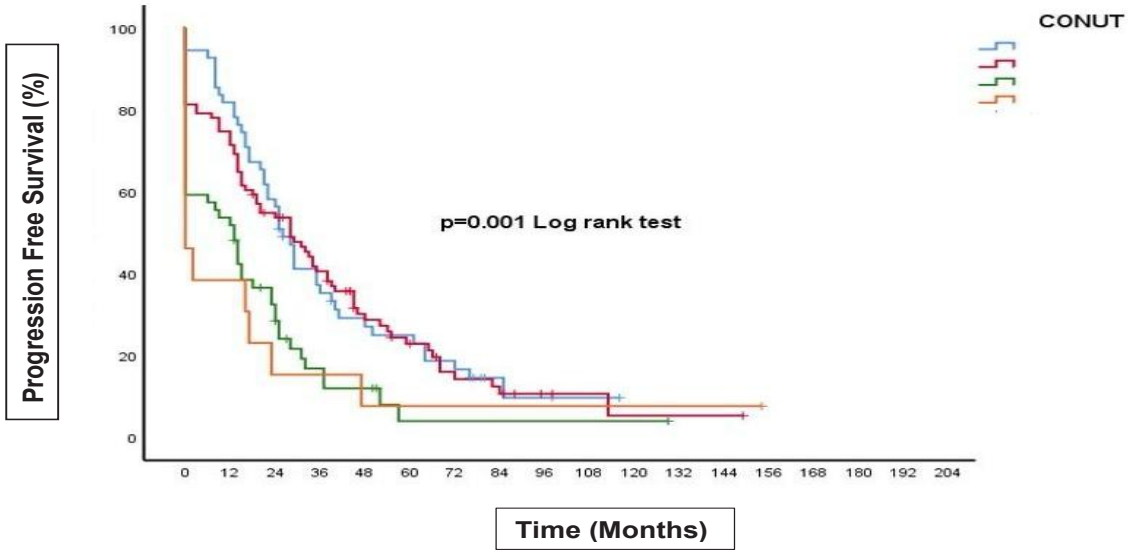

Figure 2b. PFS (%); Time (months); CONUT (normal, low, moderate, high)

Table 1a. Patient characteristics

	Median	Min-Max
Age (years)	64.0	40-89
WBC (K/uL)	6270.0	1870.0-14220.0
Lymphocytes (K/uL)	1650.0	220.0-7600.0
Hb (g/dL)	9.8	(5.5-15.8)
Albumin (g/dL)	3.47	(1.8-4.8)
LDH (U/L)	178.0	58.0-1105.0
Total cholesterol (mg/dL)	169.0	39.0-2831.0
ß2M (mg/L)	6.5	1.9-29.5

* WBC: white cell count, Hb: Hemoglobin, LDH: lactate dehydrogenase, ß2M: β2-microglobulin

Table 1b. Patient characteristics and laboratory findings

Gender	Male, 114; Female, 99
Renal dysfunction	Yes, 131; No, 82
Ig subtype	IgG Kappa, 76; IgG Lambda, 49; IgA Kappa, 17; IgA Lambda, 19; Kappa, 31; Lambda 21
R-ISS	I, 29; II, 58; III, 126
ASCT	None, 90; Once, 110; Twice, 13
CONUT	Normal, 55; Low, 91; Moderate, 54; High, 13

*R-ISS: Revised International Staging System, ASCT: Autologous stem cell transplant, CONUT: Controlling Nutritional Status

Table 1c. OS comparison according to LDH and Hemoglobin levels

Variable	2 years %	5 years %	Median (%95 CI)	*p*
Hemoglobin (gr/dl)				
<8.5	65.3	28.7	33.00 (21.78-44.21)	0.044*
>8.5	73.1	45.6	57.00 (42.71-71.28)	
Lactate dehydrogenase (U/L)				
<220	72.8	42.9	56.00 (47.36-64.63)	0.048*
≥220	67.4	36.6	30.00 (27.05-32.95)	

Kaplan Meier curve, Long rank test, *p<0.05 statistically significant

Table 1d. PFS comparison according to LDH and Hemoglobin levels

Variable	2 years %	5 years %	Median (%95 CI)	*p*
Hemoglobin (gr/dl)				
<8.5	31.3	9.0	14.00 (11.68-16.33)	0.018*
>8.5	50.3	21.7	25.00 (20.10-29.90)	
Lactate dehydrogenase (U/L)				
<220	49.2	22.2	24.00 (18.70-29.26)	0.035*
≥220	36.2	8.5	18.00 (13.96-22.03)	

Kaplan Meier curve, Long rank test, *p<0.05 statistically significant

Univariate and multivariate analysis of OS and PFS

In the univariate analysis of OS, age, renal dysfunction, R-ISS stage, ASCT status, and CONUT score (Figure 1b and Figure 2b) were found to be significant (Table 2). Variables that were significant in the univariate analyses were included in the multivariate Cox regression model. According to the model results, having a moderate CONUT score increased the risk of death by 2.21-fold (HR: 2.21, 95% CI: 1.27-3.84, *p*=0.005), while having high CONUT score increased the risk by 2.38-fold (HR: 2.38, 95% CI: 1.07-5.31, *p*=0.033). Additionally, undergoing ASCT once (HR: 0.37, 95% CI: 0.23-0.60, *p*<0.001) and twice (HR: 0.34, 95% CI: 0.15-0.78, *p*=0.012) was related to reduced risk of mortality (Table 2).

Table 2. Univariate and multivariate analysis of OS

		Univariate analysis				Multivariate analysis		
Variables		**n (%)**	**Median**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age	**≤65**	121 (56.8%)	60.0	48.43-71.56	<0.001*	Ref.		
	>65	92 (43.2%)	31.0	20.73-41.26		0.95	0.63-1.45	0.838
Renal Dysfunction	**No**	82 (38.5%)	74.0	34.63-113.36	<0.001*	Ref.		
	Yes	131 (61.5%)	33.0	34.9-41.09		1.29	0.78-2.14	0.308
R-ISS Stage	**I**	29 (13.6%)	98.0	26,37-169,62		Ref.		
	II	58 (27.2%)	63.0	50.89-75.10	0.002*	1.08	0.52-2.24	0.824
	III	126 (59.2%)	31.0	21.43-40.56		1.21	0.56-2.52	0.613
ASCT	**None**	90 (42.3%)	23.0	18.52-27.48		Ref.		
	Once	110 (51.6%)	68.0	29.48-106.51	<0.001*	0.37	0.23-0.60	<0.001*
	Twice	13 (6.1%)	74.0	49.06-98.93		0.34	0.15-.078	0.012*
CONUT	**Normal**	55 (25.8%)	66.0	26.4-105.59		Ref.		
	Low	91 (42.7%)	54.0	43.03-64.96	<0.001*	1.22	0.71-2.09	0.456
	Moderate	54 (25.4%)	27.0	21.08-32.91		2.21	1.27-3.84	0.005*
	High	13 (6.1%)	12.0	0.0-35.11		2.38	1.07-5.31	0.033*

R-ISS: Revised International Staging System, ASCT: Autologous stem cell transplant, CONUT: Controlling Nutritional Status
Kaplan Meier curve, Long rank test, cox regression, *p<0.05 statistically significant

In the univariate analysis of PFS, age, renal dysfunction, R-ISS stage, ASCT status, and CONUT score were identified as significant factors (Table 3). Variables that were significant in the univariate analyses were included in the multivariate Cox regression model. The model results indicated that having a moderate CONUT score increased the risk of progression by 1.85-fold (HR: 1.85, 95% CI: 1.18-2.89, *p*=0.007), while a high CONUT score increased the risk by 2.01-fold (HR: 2.01, 95% CI: 1.02-3.96, *p*=0.043). Moreover, undergoing ASCT once (HR: 0.41, 95% CI: 0.26-0.61, *p*<0.001) and twice (HR: 0.51, 95% CI: 0.25-0.99, *p*=0.048) was associated with a reduced risk of progression (Table 3).

Table 3. Univariate and multivariate analysis of PFS

		Univariate analysis			Multivariate analysis		
Variables		**Median**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age	**≤65**	28.0	22.17-33.82	0.001*	Ref.		
	>65	13.0	7.99-18.00		1.05	0.71-1.53	0.796
Renal Dysfunction	**No**	34.0	26.72-41.27	<0.001*	Ref.		
	Yes	15.0	12.53-17.46		1.53	1.00-2.34	0.047*
R-ISS Stage	**I**	26.0	14.18-37.82		Ref.		
	II	29.0	19.79-38.20	0.030*	0.65	0.38-1.11	0.119
	III	15.0	11.12-18.87		0.63	0.35-1.15	0.135
ASCT	**None**	1.00	-		Ref.		
	Once	32.00	25.43-38.56	<0.001*	0.41	0.26-0.61	<0.001*
	Twice	35.00	16.21-53.78		0.51	0.25-0.99	0.048*
CONUT	**Normal**	26.0	21.64-30.35		Ref.		
	Low	28.0	16.77-39.22	0.001*	0.94	0.63-1.39	0.764
	Moderate	13.0	6.93-19.06		1.85	1.18-2.89	0.007*
	High	1.0	-		2.01	1.02-3.96	0.043*

* R-ISS: Revised International Staging System, ASCT: Autologous stem cell transplant, CONUT: Controlling Nutritional Status
Kaplan Meier curve, Long rank test, cox regression, *p<0.05 statistically significant

Discussion

The CONUT score is a recent immunonutritional marker used to designate patients with malnutrition [12]. It is expressed that the CONUT score is successful in predicting poor prognosis and postoperative complications in cancer. These parameters that constitute the CONUT score are routinely measured during blood collection in daily clinical practice. The CONUT score is related to progression and mortality in patients with cancer. We studied the relationship of CONUT score and survival in patients with MM. We found that patients with high CONUT scores had reduced OS and PFS; we showed that a high CONUT score is an independent and robust prognostic index in patients with MM in our study.

The prognosis of MM, like that of other cancers, is related to some factors in the way that patient characteristics, stage of disease, cytogenetic features, and response to treatment [13]. Malnutrition is a common issue among cancer patients. It contributes not only to physical and functional impairment but also to a poorer response to therapy. The CONUT score provides valuable insight into the nutritional and immunological status of patients. Using these parameters, patients are assigned scores and categorized accordingly. The utility of the CONUT score in nutritional status, determining severity, and predicting adverse clinical outcomes has been demonstrated [7]. Furthermore, the prognostic significance of the CONUT score is known in solid organ cancers, cardiovascular diseases, and renal diseases [9, 10].

Thus, elucidating the impact of the CONUT score in hematological malignancies has recently gained impetus. Nagata et al. [14] retrospectively evaluated 476 cases diagnosed with diffuse large cell B-cell lymphoma (DLCBL), and the patient group with a CONUT score ≥4 had lower OS and PFS. Akgün Çağlıyan et al. [15] reported that a high CONUT score (≥2) pointed to lower OS and PFS in 266 patients with DLCBL. Ureshino et al. [16] noted that a low CONUT score in adult T-cell leukemia was related to better survival and may predict a favorable prognosis for transplantation. Senjo et al. [17] evaluated 174 patients with acute myeloid leukemia by omitting the lymphocyte count parameter to adapt the CONUT score and showed that the simplified CONUT score was

successful in predicting prognosis. Okamato et al. [18] evaluated the CONUT score in 64 MM patients and found that, particularly among younger patients eligible for transplantation. They expressed that the CONUT score was a prognostic index with patients having a high CONUT score (>4) showing a shorter median OS. Furthermore, Zhou et al. [19] retrospectively assessed 245 MM patients, stratifying them into three groups. They found that 5-year OS was 65.1% with a low CONUT score (≤3), 38.9% with a moderate CONUT score (4-9), and 16.6% with a high CONUT score (>9). Results confirmed that a high CONUT score was an independent risk factor for OS.

In our study, we examined 213 patients with MM in four groups according to the CONUT score: normal, low, medium and high. In our study, the median hemoglobin value was found to be 9.8 (5.5-15.8) g/dL. We performed the analysis according to hemoglobin level; median OS was 57.00 (min: 42.71-max: 71.28) months in those with hemoglobin>8.5 g/dL, and median OS was found 33.00 (min: 21.78-max: 44.21) months in those with hemoglobin <8.5. Our study has once again shown that the level of anemia is an indicator of prognosis and survival at the time of diagnosis. We performed according to LDH level; median OS was 30.00 (min: 27.05-max: 32.95) months in those with LDH ≥220, and median OS was 56.00 (min: 47.36-max: 64.63) months in those with LDH <220. We detected that the median PFS in patients with LDH ≥220 was 18.00 (min: 13.96-max: 22.03) months, and with LDH<220, it was 24.00 (min: 18.70-max: 29.26) months. In our study, we detected the median OS in the patient group with R-ISS stage I was 98 (min: 26.37-max: 269.62) months, with stage II the median OS was 63 (min: 50.89-max: 75.10) months, and with stage III the median OS was 31 (min: 21.43-max: 40.56) months, consistent with the literature. In the survival analyses, we detected median OS with a normal CONUT score was 66.00 (min: 26.40-max: 105.59) months, median OS with a low CONUT score was 54.00 (min: 43.03-max: 64.96) months, median OS with a moderate CONUT score was 27.00 (min: 21.08-max: 32.91) months, and median OS with a high CONUT score was 12.00 (min: 0.00-max: 35.11) months. We observed that a high CONUT score was related to decreasing OS. We found that the risk of mortality with a moderate CONUT score increased by 2.21 fold and with a high CONUT score increased by 2.38 fold. We found that 5-year OS was 41.6% and 5-year PFS was 18.6% in our study with 213 MM patients. The results indicated that having a moderate CONUT score increased the risk of progression by 1.85-fold, while a high CONUT score increased the risk by 2.01-fold. We detected a negative correlation between the CONUT score and both OS and PFS. Moreover, undergoing ASCT was associated with a reduced risk of progression. We showed that ASCT remains a beneficial therapy in patients with MM. Furthermore, significant differences were noted between high CONUT scores and factors in the way that age, renal dysfunction, and R-ISS stage. We found a difference between ≤65 and >65 years old in terms of OS and PFS. We showed that if the patients had renal dysfunction and advanced stage, they had reduced OS and PFS and a high CONUT score. Overall, our results noted that the CONUT score is a strong index of poor prognosis in MM.

The CONUT score is an easy method to calculate; it can be implemented during routine blood collection in MM patients at diagnosis. A high CONUT score is related to reducing survival. We proved that the CONUT score is an independent, useful, and poor prognostic index in MM. However, we hope for prospective studies with larger patient groups to further validate the long-term reliability and validity of the CONUT score.

Limitation

We designed our study as a retrospective and single centre. There was no record about calorie and diet uptake. We did not evaluate body mass index at during the diagnosis. There were some differences between the types of therapies. Some patients were applied therapies at an earlier line. This condition was related to accessibility and drug payment instructions and off-label approval at different periods.

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Authors contributions: E.N.C. and G.A.C. contributed equally.

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