ULUSLARARASI HEMATOLOJI-ONKOLOJI DERGISI ARTICLE International Journal of Hematology and Oncology

Effects of Metabolic Parameters on The Clinical Course of Hematological Malignancies

Burak BIRSOY[1], Umit Yavuz MALKAN[2]

[1] Ankara Etlik State Hospital, Department of Gastroenterology
[2] Hacettepe University, Faculty of Medicine, Department of Hematology

ABSTRACT

Metabolic syndrome (MS), characterized by insulin resistance, obesity, dyslipidemia, and hypertension, is linked to various systemic diseases and hematological malignancies. This study aimed to determine the effects of MS and body mass index (BMI) on prognosis, treatment response, and survival rates in hematological malignancies. A retrospective analysis was conducted on 89 patients treated at Ankara Diskapi Yildirim Beyazit Training and Research Hospital between 2020-2021. Among the patients, 7 had acute lymphoblastic leukemia (ALL), 27 had acute myeloid leukemia (AML), 13 had diffuse large B-cell lymphoma (DLBCL), 6 had Hodgkin lymphoma (HL), 10 had chronic lymphocytic leukemia (CLL), 11 had chronic myeloid leukemia (CML), and 15 had multiple myeloma (MM). High BMI was associated with refractory disease in ALL patients ($p= 0.03$). AML patients with MS had higher ECOG performance scores ($p= 0.045$). Overweight DLBCL patients exhibited elevated LDH levels ($p< 0.001$), while low-weight DLBCL patients had higher lymphocyte and white blood cell counts ($p= 0.023$, $p< 0.001$). Overweight and obese CML patients had higher basophil counts and uric acid levels ($p= 0.003$). In MM patients, overweight and obese group showed higher R-ISS scores and more SLIM criteria ($p= 0.048$, $p= 0.018$), and the obese group had higher sedimentation rates ($p= 0.01$). ECOG performance score was higher in MM patients with MS ($p= 0.047$). In conclusion, MS and high BMI are associated with adverse prognostic factors in hematological malignancies. Therefore, monitoring and managing MS and BMI are crucial for improving treatment outcomes and survival rates.

Keywords: Metabolic syndrome, Hematological malignancies, Prognosis

INTRODUCTION

Metabolic Syndrome (MS) arises from overeating and a sedentary lifestyle, characterized by insulin resistance (IR), abdominal obesity, dyslipidemia, and high blood pressure, often accompanied by impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). This syndrome is associated with various systemic diseases.[1,2] Due to the increasing prevalence of obesity and diabetes mellitus, the frequency of MS is also increasing.[3] Numerous studies have found an association between MS and several hematological malignancies.[4] Research exploring the relationship between MS, obesity, and cancer development has revealed the involvement of different metabolic pathways.[5] Visceral fat accumulation and obesity contribute to cancer development by increasing TNFα levels, which trigger the increase of NF-κB and other inflammatory cytokines, promoting malignancy. Pro-inflammatory molecules such as IL-6 have been shown to increase in the body with higher Body Mass Index (BMI), playing a role in activating the STAT3 protein, which contributes to cancer development.[6,7] Another inflammatory cytokine, PAI1, has been linked to obesity and carcinogenesis.[8] Increases in leptin levels and decreases in adiponectin levels, associated with increased fat tissue, have also been implicated in cancer development. Moreover, individuals with obesity and MS often develop insulin resistance in many tissues, typically resulting in hyperglycemia.

As a compensatory mechanism, pancreatic beta cells secrete more insulin, perpetuating elevated insulin signaling and contributing to tumorigenesis. Additionally, high insulin resistance and obesity have been shown to reduce the response to cancer treatment and lead to poor prognoses.[9-11] Several meta-analyses have clearly demonstrated the relationship between MS and hematological malignancies, with some subgroup analyses revealing a strong significant association between high BMI and hematological malignancies.[12] This study aims to evaluate the relationship between MS and hematological malignancies.

PATIENTS AND METHOD

Between September 1, 2020, and September 1, 2021, a total of 89 patients were included in the study, who presented to the Hematology Clinic of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital for diagnosis, follow-up, and treatment purposes. Among them, there were 7 patients with Acute Lymphoblastic Leukemia (ALL), 27 with Acute Myeloid Leukemia (AML), 13 with Diffuse Large B-Cell Lymphoma (DLBCL), 6 with Hodgkin Lymphoma (HL), 10 with Chronic Lymphocytic Leukemia (CLL), 11 with Chronic Myeloid Leukemia (CML), and 15 with Multiple Myeloma (MM). Patients diagnosed with Acute Promyelocytic Leukemia, Follicular Lymphoma, Hairy Cell Leukemia, and T-cell Lymphoma were excluded from the study due to an insufficient number of cases for statistical analysis. Data were obtained from the hospital's digital database and patients' medical records. Various parameters of the patients were assessed, including file number, gender, date of diagnosis, refractory status, relapse status, occurrence of death and its date if applicable, stage of disease at diagnosis and at presentation to our clinic, initiated treatments, number of different treatments administered, treatment response post-therapy, timing of response if achieved, date of bone marrow biopsy for evaluation post-treatment, observed side effects post-treatment, presence of Minimal Residual Disease (MRD) negativity, timing of MRD negativity if present, presence of resistance to the given drug, existence of mutation causing resistance if applicable, and the date of the patient's last visit.

Additionally, at the time of diagnosis, parameters such as white blood cell count, hemoglobin level, platelet count, creatinine level, blast percentage in bone marrow, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total protein, albumin, sedimentation rate, and C-reactive protein (CRP) levels were evaluated. Other parameters included Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, spleen size, vitamin D measurement, uric acid level, fasting blood glucose level, waist circumference, height and weight, Body Mass Index (BMI), systolic and diastolic blood pressure, HbA1c, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, very low-density lipoprotein (VLDL), and total cholesterol levels. Moreover, it was assessed whether the patient underwent autologous or allogeneic bone marrow transplantation, the conventional cytogenetic results of the patient, cytogenetic risk group, disease status at the last visit, presence of treatment-related comorbidities, additional comorbidities at the time of diagnosis, and detailed information regarding the treatments given to the patient, all of which were obtained from patient records and the database.

Additionally, in Chronic Myeloid Leukemia (CML) patients, the Sokal score, basophil count, and the usage of tyrosine kinase inhibitors were assessed; in Acute Lymphoblastic Leukemia (ALL) patients, the immunophenotypic group, presence of extramedullary involvement and its site if present; in Acute Myeloid Leukemia (AML) patients, whether the disease was primary or secondary, in Diffuse Large B-Cell Lymphoma (DLBCL) patients, the beta-2 microglobulin value, International Prognostic Index (IPI) and Revised International Prognostic Index (R-IPI) scores, presence of double-hit or triple-hit at diagnosis, B-symptoms, presence of bulky disease, in Follicular Lymphoma patients, FLIPI-1 and FLIPI-2 scores and Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, presence of central nervous system involvement and the number of involved nodal areas, in Hodgkin Lymphoma patients, IPS-3 and IPS-7 values, Deauville score post-treatment, in Multiple Myeloma patients, calcium, phosphorus, beta-2 microglobulin levels, type of M protein and its lev-

Table 1. Comparison of categorical data of acute lymphoblastic lymphoma patients by body mass index groups

Parameter	Body mass index group			
	Normal	Overweight	Obese	p
B-ALL/Ph+ ALL	2/1	2/1	1/0	0.792
No Refractory Disease/Refractory Disease	3/0	3/0	0/1	0.030
No Extramedullary Involvement/Extramedullary Involvement	2/1	2/1	1/0	0.792
No Death/Death	3/0	1/2	0/1	0.118
No Relapse/Relapse	3/0	3/0	1/0	N/A
Negative Minimal Residual Disease/Positive Minimal Residual Disease	0/3	1/2	0/1	0.459
Male/Female	3/0	2/1	1/0	0.459
No Hypertension/Hypertension	3/0	2/1	1/0	0.459
Cytogenetic Risk Group: Poor/Intermediate/High	1/1/0	0/0/3	0/1/0	0.112
No Treatment-Related Mortality/Mortality	3/0	2/1	0/1	0.155
Death due to Infection/Cardiac Causes	0/0	1/1	1/0	0.667

el, International Staging System (ISS) and Revised International Staging System (R-ISS) criteria, bone marrow plasma cell ratio, presence of CRAB and SLiM criteria, and presence of osteolytic bone lesion were evaluated.

The diagnosis criteria for Metabolic Syndrome were based on the Adult Treatment Panel 3 (ATP 3) diagnostic criteria.

This study has been accepted as Burak Birsoy's internal medicine specialization thesis. Ethical approval was obtained from the Ethics Committee of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 10.08.2020 / No: 93/05).

Statistical Analysis

All statistical analyses were performed using IBM© SPSS© Statistics Version 25.0 for Windows (Armonk, NY: IBM Corporation, 2017). Initially, descriptive statistics were conducted for patient-related data. Categorical variables were analyzed primarily using the chi-square test or Fisher's exact test. For continuous variables, distribution analysis was performed initially. The distribution of continuous variables was analyzed using the Kolmogorov-Smirnov test. Normally distributed continuous variables were examined using the t-test or ANOVA. Non-normally distributed variables were analyzed using the Mann-Whitney U test or Kruskal-Wallis test. Kaplan-Meier analysis was conducted for survival analysis. A significance level of $p< 0.05$ was considered statistically significant.

RESULTS

We have analyzed 89 patients included in our study. The breakdown of the patient diagnoses is as follows: 7 had ALL, 27 had AML, 13 had DLBCL, 6 had HL, 10 had CLL, 11 had CML, and 15 had MM. We performed statistical analyses within each disease group. For ALL patients, we examined the relationship between categorical data and the presence of MS. The analysis showed no significant statistical relationship between MS presence and the categorical data of ALL patients. However, when comparing continuous data of ALL patients with the presence of MS, we found a significant relationship between the patients' weight and MS, with $p= 0.048$. MS was more common in overweight patients. When comparing categorical data of ALL patients based on BMI groups, we found a significant relationship between the presence of refractory disease and obesity, with $p= 0.030$ (Table 1). As BMI increased, the incidence of refractory disease also increased. No significant relationship

Table 2. Comparison of categorical data of acute myeloid leukemia patients with metabolic syndrome

Parameter	No Metabolic Syndrome	Metabolic Syndrome	p
Primary De Novo AML/Secondary AML	8/3	7/9	0,137
No Relapse/Relapse	9/2	16/2	0,157
No Death/Death	6/5	8/8	1
Response After Induction Therapy: Refractory/Partial/Complete	5/2/3	1/5/3	0,142
ECOG Score: 0/1/2/3	6/2/2/1	1/7/6/2	0,045
Male/Female	7/4	6/10	0,182
Cytogenetic Risk Group: Poor/Intermediate/Good	1/3/5	2/2/4	0,745
Status at Last Follow-Up: Primary Refractory/ Partial Response/Complete Response	6/3/2	7/6/3	0,834
No Treatment-Related Mortality/Mortality	9/2	13/3	0,970
Cause of Death: Relapse/Infection/Cardiac/ Intracranial Hemorrhage	1/3/0/1	1/5/1/1	0,837
Comorbidity at Diagnosis: Heart Failure/Diabetes Mellitus/ Chronic Kidney Disease/Others	0/1/0/3	1/7/1//6	0,636

was found between other categorical data of ALL patients and BMI groups. Additionally, no significant relationship was observed between the continuous data of ALL patients and BMI groups. In the survival analysis for ALL patients, the average survival time was 41±0 days for those without MS and 306.667±148.187 days for those with MS, with p= 0.083, indicating no statistically significant relationship. Similarly, no significant relationship was found between BMI groups and average survival.

A significant relationship was found between ECOG performance score and MS in the AML patient group. Patients with MS had a significantly higher ECOG performance score (p= 0.045) (Table 2). No statistically significant results were obtained for other categorical data in AML patients. When comparing categorical data of AML patients based on BMI groups, a significant relationship was found between gender and MS, with MS being more common in females (p< 0.001). No significant relationship was found between other categorical data and BMI. Additionally, no significant results were obtained when comparing the continuous data of AML patients with BMI.When comparing continuous data of AML patients with MS, a significant relationship was found between HbA1c levels and MS (p= 0.023). MS was more common in patients with higher HbA1c levels. No significant relationship was found between MS and other continuous data.In the survival analysis of AML patients, the average survival time was 225.925±46.201 days for patients without MS and 339.339±92.016 days for patients with MS. No significant difference in average survival was found between the two groups (p= 0.960). When examining the relationship between MS presence and disease-free survival, no statistically significant relationship was found (p= 0.05). When evaluating the relationship between BMI and average survival, the results were as follows; normal BMI group 209.2±45.788 days, overweight group 174.5±26.414 day, obese group 440.214±120.219 days, morbidly obese group 186±0 days. No significant relationship was found between BMI and average survival (p= 0.426). Similarly, no significant relationship was found between BMI and disease-free survival (p= 0.204).

No significant data were obtained when comparing the categorical data of DLBCL patients with the presence of MS. Similarly, no statistically sig-

Table 3. Comparison of continuous data of diffuse large B-cell lymphoma patients with Body Mass Index Groups

	Body Mass Index Groups					
Parameter	**Underweight**	**Normal Weight**	**Overweight**	**Obese**	**Morbidly Obese**	**p**
White Blood Cell Count (µL)	44540 (44540-44540)	7020 (3100-8290)	9730 (6930-12530)	7940 (5500-15440)	9865 (9790-9940)	<0,001
Absolute Lymphocyte Count (µL)	12780 (12780-12780)	220 (140-2430)	5135 (990-9280)	1360 (110-3720)	2070 (720-3420)	0,023
Lymphocyte Ratio (%)	28,7 (28,7-28,7)	7,1 (2-29,30)	44,2 (14,30-7410)	13,8 (7,7-46,9)	21,3 (7,7-34,9)	0,605
Hemoglobin (g/dl)	6,7 (6,7-6,7)	9,6 (8,4-13,8)	11,05 (10,7-11,4)	13,1 (11,3-14,7)	11,75 (10,3-13,2)	0,112
Platelet Count (µL)	26000 (26000-26000)	312000 (31000-493000)	258500 (136000-381000)	240000 (144000-477000)	252500 (216000-289000)	0,743
Creatinine (mg/dl)	0,59 (0,59-0,59)	0,87 (0,68-1,51)	1,11 (0,93-1,29)	0,84 (0,69-1,21)	0,975 (0,41-1,54)	0,842
BUN (mg/dl)	17 (17-17)	40,9 (32-73)	35,5 (25-46)	27,7 (23,10-71)	32,15 (17-47,3)	0,747
ALT (U/L)	133 (133-133)	12 (9,5-17)	39 (12-66)	37,3 (11,2-191)	17,4 (15-19,8)	0,330
AST (U/L)	220 (220-220)	22 (12,5-22)	31 (23-39)	22,2 (16,1-176)	13,75 (12-15,5)	0,055
CRP (mg/L)	45,77 (45,77-45,77)	183 (3,85-27,40)	10,83 (8,27-13,39)	24,3 (2,07-101,21)	2,465 (2,40-2,53)	0,214
Sedimentation (mm/H)	39 (39-39)	39 (8-72)	56.5 (39-74)	12 (11-47)	21 (20-22)	0.396
Total Protein (g/dl)	44.80 (44.80-44.80	63 (53.20-68.6)	72.55 (71.80-73.30)	79.7 (47-88.7)	66.7 (57.6-75.8)	0.353
Albumin (g/dl)	29 (29-29)	33,2 (30-43,1)	39,4 (39,2-39,6)	40,2 (29,3-47,3)	36,8 (33,6-40)	0,669
LDH (U/L)	5095 (5095-5095)	294 (258-1480)	425,5 (143-708)	266 (126-619)	210 (190-230)	<0,001
Urik Acid (mg/dl)	2,1 (2,1-2,1)	10,9 (7-11,9)	5,16 (5,10-5,22)	4,3 (3-9,91)	6,9 (6,5-7,30)	0,084
Beta 2 Microglobulin (mg/dl)	3,19 (3,19-3,19)	7,11 (2,42-8,77)	4,345 (3,2-5,49)	2,34 (2,17-3,42)	2,855 (1,74-3,97)	0,221
Glucose (mg/dl)	92 (92-92)	122 (112-177)	152,5 (101-204)	116 (90-300)	181 (163-199)	0,853
Waist Circumference (cm)	77 (77-77)	87 (76-89)	102,5 (93-112)	112 (92-133)	127 (112-142)	0,063
HbA1c (%)	5,7 (5,7-5,7)	5,8 (5,2-6,4)	7,15 (6,1-8,2)	6,6 (5,6-8,8)	7,6 (6,4-8,2)	0,498
LDL Cholesterol (mg/dl)	52,4 (52,4-52,4)	92,2 (10,8-170,2)	120,75 (90,50-151)	114,4 (60,2-134,2)	144,05 (127,2-160,9)	0,594
HDL Cholesterol (mg/dl)	20,22 (20,22-20,22)	28,3 (16-47,7)	39 (34-44)	36 (23,1-64,5)	32,7 (32,4-33)	0,793
VLDL Cholesterol (mg/dl)	12,68 (12,68-12,68)	33,38 (29,7-42,42)	29,6 (25,4-33,8)	28,7 (11,22-52,38)	47,7 (24,46-70,94)	0,512
Total Cholesterol (mg/dl)	85,3 (85,3-85,3)	216,4 (80,9-248,9)	218,2 (218-218,4)	166,2 (112-264,8)	208,1 (194,2-222)	0,514
Triglycerides (mg/dl)	63,4 (63,4-63,4)	166,9 (148,5- 212,1)	148 (127-169)	143,5 (56,1-261,9)	238,5 (122,3-154,7)	0,512
Systolic Blood Pressure (mm/hg)	140 (140-140)	120 (110-140)	125 (120-130)	140 (100-160)	150 (130-170)	0,691
Diastolic Blood Pressure (mm/hg)	90 (90-90)	80 (65-90)	85 (80-90)	80 (60-100)	100 (90-110)	0,505

nificant relationship was found when comparing the categorical data of DLBCL patients with BMI groups. When comparing the continuous data of DLBCL patients with BMI groups, a significant relationship was found between white blood cell count and BMI groups ($p< 0.001$). As BMI increased, white blood cell count also increased. A similar significant relationship was found between BMI and absolute lymphocyte count ($p= 0.023$). Additionally, a significant relationship was found between LDH levels and BMI groups ($p< 0.001$) (Table 3). When comparing the continuous data of DLBCL patients with the presence of MS, a significant relationship was found between platelet count and MS ($p= 0.048$). A significant relationship was also found between HbA1c levels and MS ($p= 0.035$). No significant relationship was found between other continuous data and MS. In the survival analysis of DLBCL patients, the average survival time was 160.667±69.667 days for patients without MS. For patients with MS, the average survival time was 806.114±531.644 days. No significant relationship was found between the presence of MS and survival ($p= 0.257$).

Table 4. Comparison of continuous data of chronic myeloid leukemia patients with Body Mass Index

	Body Mass Index Groups			
Parameter	**Normal**	**Overweight**	**Obese**	**p**
White Blood Cell Count (µL)	63340 (15570-111110)	218580 (218580-218580)	73955 (8490-208500)	0,166
Basophil Count (µL)	3415 (290-6540)	17920 (17920-17920)	3025 (60-6670)	0,003
Hemoglobin (g/dl)	12,1 (11,5-12,7)	9,4 (9,4-9,4)	11,9 (7-14,2)	0,661
Platelet (µL)	165500 (138000-1933000)	336000 (336000-336000)	258500 (14000-888000)	0,683
Creatinine (mg/dl)	0,91 (0,78-1,04)	0,7 (0,7-0,7)	0,95 (0,84-1,45)	0,392
BUN (mg/dl)	28,80 (26,6-31)	18 (18-18)	38,65 (25,3-49,6)	0,141
Bone Marrow Blast (%)	3,5 (3-4)	7 (7-7)	3 (1-7)	0,223
ALT (U/L)	32,25 (25,5-39)	6 (6-6)	25,05 (10-30)	0,091
AST (U/L)	28,6 (22-35,2)	16 (16-16)	21,3 (8-29)	0,366
LDH (U/L)	716,5 (194-1239)	1122 (1122-1122)	526,5 (225-1335)	0,509
Spleen Size at Diagnosis (cm)	20,10 (16-24)	16 (16-16)	13,9 (12-23)	0,482
Uric Acid (mg/dl)	6,50 (6,50-6,50)	12,2 (12,2-12,2)	6,2 (5,1-8,2)	0,003
Systolic Blood Pressure (mmHg)	110 (110-110)	110 (110-110)	130 (110-150)	0,118
Diastolic Blood Pressure (mmHg)	75 (70-80)	70 (70-70)	80 (70-95)	0,530
HDL Cholesterol (mg/dl)	37,3 (24,5-50,10)	29,8 (19,8-19,8)	38,9 (7,08-53,8)	0,893
Triglycerides (mg/dl)	105,85 (86,30-125,4)	171,5 (171,5-171,5)	165,2 (74-264,8)	0,648
Glucose (mg/dl)	126 (74-178)	89 (89-89)	105 (73-142)	0,664
Waist Circumference (cm)	92 (84-100)	98 (98-98)	105 (90-121)	0,390
HbA1c (%)	6,9 (5,8-8)	5 (5-5)	6,25 (5,6-7,5)	0,216
LDL Cholesterol (mg/dl)	53,65 (42,8-64,5)	85,1 (85,1-85,1)	100,85 (63,20-130)	0,090
VLDL Cholesterol (mg/dl)	21,17 (17,26-25,08)	34,3 (34,3-34,3)	33,04 (14,8-52,96)	0,648
Total Cholesterol (mg/dl)	106,3 (91,20-121,40)	145,5 (145,5-145,5)	171,15 (121,4-236,2)	0,136

In patients with Hodgkin's lymphoma (HL), a significant relationship was found between C-reactive protein (CRP) levels and body mass index (BMI) groups ($p< 0.001$). Similarly, a significant relationship was observed between sedimentation levels and BMI groups ($p= 0.005$). Additionally, beta-2 microglobulin levels showed a significant relationship with BMI groups ($p= 0.022$). No significant relationship was found between other continuous variables and BMI groups. However, when comparing the continuous variables of HL patients with metabolic syndrome, no significant results were obtained, likely due to the absence of observed fatalities among HL patients, making it impossible to perform mean survival statistics.

In patients with chronic lymphocytic leukemia (CLL), no statistically significant results were obtained when comparing with MS. Similarly, no significant relationship was found between CLL patients' categorical data and BMI. Regarding continuous data, a significant relationship was found between height and MS ($p= 0.021$). Moreover, a significant relationship was observed between HDL cholesterol levels and BMI ($p= 0.042$), glucose levels and BMI ($p= 0.002$), and waist circumference and BMI ($p= 0.029$). Additionally, a significant relationship was found between HbA1c levels and BMI ($p= 0.027$). No significant relationship was found between other continuous variables and BMI.

Table 5. Comparison of categorical data of multiple myeloma patients with Body Mass Index

Parameter	Body Mass Index Group				
	Underweight	Normal	Overweight	Obese	p
No Death/Death	1/0	4/0	4/1	5/0	0,543
No Relapse/Relapse	1/0	4/0	5/0	5/0	N/A
Autologous Bone Marrow Transplantation Absent/Exist	1/0	3/1	5/0	3/2	0,421
ECOG Score 0/1/2/3/4	0/0/0/1/0	1/1/1/1/0	0/1/2/1/1	0/1/4/0/0	0,499
Male/Female	1/0	4/0	3/2	4/1	0,475
Hypertension Absent/Exist	0/1	3/1	1/4	2/3	0,315
M Protein Type Ig G Lambda/Ig A Kappa/Ig G Kappa/Kappa Light Chain/Lambda Light Chain	0/1/0/0/0	3/1/0/0/0	2/0/2/0/1	0/0/3/1/1	0,138
ISS Score 1/2/3	0/0/1	1/0/3	1/0/4	1/1/3	0,884
R-ISS Score 1/2/3	0/0/0	1/0/1	1/0/3	0/3/0	0,048
Disease Status Before Autologous Bone Marrow Transplantation Complete Response/Partial Response/Progressive Disease	0/1/0	1/1/2	0/3/2	2/2/1	0,609
Disease Status at Last Visit Complete Response/Partial Response/Progressive Disease	0/1/0	1/1/2	0/3/2	2/2/1	0,609
Treatment-Related Mortality Absent/Exist	1/0	4/0	4/1	5/0	0,543
CRAB Factors Positive A/B/RA/AB/RAB/CRAB	0/0/0/0/0/1	2/0/0/2/0/0	0/1/2/1/0/1	0/2/0/0/2/1	0,095
SLIM Criteria Positive L/M/SL/M/SLIM	0/0/0/0/1	3/1/0/0/0	2/0/2/1/0	1/2/0/2/0	0,018
Presence of One or More Osteolytic Bone Lesions Absent/Exist	0/1	2/2	2/3	0/5	0,290
Presence of Bone Involvement Absent/Exist	1/0	2/2	3/2	5/0	0,290

In patients with chronic myeloid leukemia (CML), no significant relationship was found when comparing categorical data with MS. Furthermore, no significant relationship was observed between treatment response times at 3, 6, and 9 months and MS. Similarly, no significant results were obtained when comparing CML patients' categorical data. However, when comparing continuous data with MS, a significant relationship was found between alanine transaminase (ALT) levels and MS (p= 0.023), as well as between aspartate transaminase (AST) levels and MS (p= 0.017). Additionally, a significant relationship was found between basophil count and BMI groups (p= 0.003) and between uric acid levels and BMI groups (p= 0.003) (Table 4).

When comparing the categorical data of Multiple Myeloma (MM) patients with Multiple Sclerosis (MS), a significant association was found between ECOG score and MS (p= 0.047). However, no significant association was observed between other variables and MS. In the comparison of MM patients' categorical data with Body Mass Index (BMI), a significant relationship was found between R-ISS score and BMI (p= 0.048). Similarly, a significant association was detected between SLIM criteria and BMI (p= 0.018) (Table 5). Regarding the comparison of MM patients' continuous data with BMI, a significant relationship was observed between sedimentation rate and BMI (p= 0.010). Additionally, a significant association was found between waist circumference and BMI (p=

0.020). In the comparison of MM patients' continuous data with MS, a significant association was found between HbA1c level and MS (p= 0.006). Similarly, a significant relationship was noted between LDL and MS (p= 0.010). Moreover, a significant association was observed between total cholesterol and MS (p= 0.005). Analysis of the average survival statistics revealed no significant association between BMI and average survival in MM patients (p= 0.572). Similarly, no significant relationship was found between average survival and MS in MM patients (p= 0.564).

DISCUSSION

Metabolic Syndrome (MS) is a clinicopathological syndrome involving complex pathophysiological mechanisms, arising from decreased energy expenditure, sedentary lifestyle, reduced physical activity, and genetic factors. It primarily comprises four main components: abdominal obesity, insulin resistance, hypertension, and dyslipidemia.[13,14] Recently, the increase in MS prevalence has drawn attention due to decreased physical activity, increased smoking, rise in processed food consumption, and elevated intake of saturated fatty acids and sugars.

Examining MS prevalence in Turkey, data from the Turkey Metabolic Syndrome Research Group in 2007 revealed a prevalence of 39.6% in females and 27% in males.[15] As a consequence of the increasing MS prevalence, there has been a noticeable rise in hypertension, cardiovascular diseases, type 2 diabetes mellitus (DM), and various cancer types.[16] Numerous studies have demonstrated a close association between MS and both hematological and non-hematological cancers. Particularly, several meta-analyses have directly linked MS with Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Non-Hodgkin's Lymphoma (NHL), Chronic Myeloid Leukemia (CML), Multiple Myeloma (MM), Hodgkin's Lymphoma (HL), and B-cell lymphoma.[4,12,17] In the pathogenesis of MS-related hematological cancers, increased levels of cytokines such as TNFα, NF-κB, IL-6, STAT3, and PAI1, along with elevated leptin levels, decreased adiponectin levels, and increased insulin resistance, have been identified to play significant roles.[6-8,18] In our study, we aimed to investigate the association between hematological malignancies and MS, and if present, elucidate the nature of this relationship.

In our study, the rate of refractory disease was found to be higher in the obese group compared to the normal and overweight groups among ALL patients (p= 0.030). This finding aligns with the results of Butturini et al., who conducted a study with a total of 3917 patients, where a significant association was observed between obesity and the incidence of refractory disease and poor prognosis (p< 0.001).[19]

In a study conducted by Papageorgiou et al. in 2020, involving 687 patients in Greece, it was demonstrated that among AML patients, those with an ECOG score of 2 or higher had significantly higher average overall survival and progression-free survival compared to patients with an ECOG score below 2. Furthermore, the study indicated a lower disease response in the group with higher ECOG scores.[20] In our study, among AML patients, it was observed that the ECOG performance score was higher in the group with MS compared to the group without MS (p= 0.045). This suggests a decrease in treatment response and average survival among patients with MS.

In a cohort study conducted by Rabinovich et al. in the United States, involving 31 patients with Diffuse Large B-cell Lymphoma (DLBCL), Anti-CD19 chimeric antigen receptor T-cell therapy (CAR-T) was administered, and the impact of lactate dehydrogenase (LDH) levels on prognosis was investigated. It was demonstrated that LDH levels measured before cell infusion exceeding 400 U/L and LDH levels measured before lymphodepletion exceeding 440 U/L had a negative impact on patients' average survival and treatment responses.[21] In our study, a significant relationship was found between Body Mass Index (BMI) groups and LDH levels (p< 0.001). There was one patient in the low-weight group, with an LDH level of 509.5. However, particularly notable was the high LDH levels observed in the overweight group. The median LDH level in the overweight group was determined to be 425.5 U/L, supporting the significance of high BMI in LDH elevation. In a multicenter

study conducted by Feng et al., comprising a total of 1206 DLBCL patients from six different studies, a low absolute lymphocyte count was found to be associated with poor prognosis. Additionally, in the same study, a low absolute lymphocyte count was correlated with progression-free survival ($p< 0.001$).[22] In a study by Han et al. in China, involving 45 DLBCL patients, the total white blood cell count subgroups were analyzed, and a decrease in all white blood cell subgroups was found to be associated with poor prognosis in DLBCL.[23] Our study revealed a statistically significant relationship between BMI and total white blood cell and absolute lymphocyte counts in DLBCL patients. Total white blood cell and absolute lymphocyte counts were higher in the low-weight group and lower in the other groups ($p= 0.023$).

In assessing the risk of Chronic Myeloid Leukemia (CML), various scoring systems such as Sokal, Hasford, and EUTOS are employed. Among these systems, the Hasford and EUTOS scoring systems notably highlight the importance of basophil count. A multitude of publications in the literature demonstrate the association between high basophil count and poor prognosis in CML. In a study conducted by Denburg et al. in Canada, 47 patients were evaluated. Specifically, the basophil cells of these 47 CML patients were examined in a laboratory setting for basophil growth index and differentiation levels. It was noted that patients with a positive basophil growth index exhibited a higher basophil count in peripheral blood. Moreover, these patients demonstrated higher rates of blast crisis and mortality over a two-year follow-up period, with statistically significant results obtained from the analyses ($p< 0.001$).[24] Our study also identified a significant relationship between basophil count and Body Mass Index (BMI) in CML patients ($p= 0.003$). In this context, CML patients were categorized into normal, overweight, and obese groups based on their BMI. The basophil count was found to be significantly higher in the overweight and obese groups compared to the normal group. Another study, conducted by Vonka et al. in the Czech Republic, involved 29 CML patients and 28 normal individuals. This study investigated the activities of enzymes indoleamine 2,3-dioxygenase 1 and 2, along with tryptophan 2,3-dioxygenase, which have been previously implicated in various malignancies. Enzyme activities were assessed based on the kynurenine/tryptophan ratio, suggesting a potential association between increased kynurenine levels, uric acid, and tumor burden in CML patients.[25] Consistently, our study revealed a significant correlation between BMI and uric acid levels ($p= 0.003$). Particularly, elevated uric acid levels were observed in the overweight and obese groups, hinting at a possible link between uric acid levels and tumor burden, as well as BCR-ABL levels, in patients with higher BMI. Thus, the elevated uric acid levels in patients with higher BMI may serve as an indirect indicator of tumor burden.

In a retrospective study conducted by Udupa et al. in India, the presence of high-risk genetic abnormalities in Multiple Myeloma (MM) patients was compared with the Revised International Staging System (R-ISS) score. Among the entire population of 117 individuals, genetic abnormalities were detected in 16.23% of cases, while in the group classified as R-ISS 3, a higher incidence of 31.62% was observed.[26] The literature provides ample evidence supporting the robust prognostic value of R-ISS in MM staging.[27] In our study, MM patients were categorized into four groups based on their Body Mass Index (BMI): underweight, normal weight, overweight, and obese. A significant association was found between BMI and R-ISS ($p= 0.048$), particularly with higher R-ISS scores noted in the overweight and obese groups. This underscores the impact of BMI on MM prognosis, indicating a worsened prognosis with higher BMI. The utility of SLiM criteria in MM diagnosis has been emphasized in numerous studies, with a consensus emerging in the literature supported by substantial evidence.28 Our study also revealed a significant relationship between BMI groups and SLiM criteria ($p= 0.018$), with a higher prevalence of 2 or 3 SLiM criteria observed in the overweight and obese groups. This suggests that BMI influences SLiM criteria at the time of diagnosis. In a study by Alexandrakis et al. in Greece involving 67 participants, including 42 newly diagnosed MM patients and 25 controls, elevated sedimentation rate was found to be associated with reduced overall survival, highlighting its prognostic value.[29] Similarly, our study showed a significant association

between BMI groups and sedimentation rate (p= 0.01), with markedly higher sedimentation rates observed in the obese group. Furthermore, a study by Afram et al. in Sweden, which included 156 MM patients, demonstrated a poorer prognosis and treatment response, particularly in patients with an ECOG performance status of 2 or higher.[30] Similarly, our study identified a significant association between MM and ECOG performance status, with higher scores observed in the MS patient group (p= 0.047).

In a previous analysis, vitamin D levels suggested to play an important role in the prognosis of hematological malignancies. It was shown that diffuse large B cell lymphoma cases with low vitamin D levels, had higher beta 2 microglobulin levels.[31] Also in chronic lymphocytic leukemia cases with those with low vitamin D levels were found to have higher absolute lymphocyte count and lymphocyte ratios.[31] Moreover, multiple myeloma cases with low vitamin D levels were found to have more CRAB symptoms.[31] On the other hand, the relationship between vitamin D and metabolic parameters are investigated and reported in the literature.[32] In the future studies, the relationship of metabolic parameters and hematological malignancies may be considered with the context of the effects of vitamin D altogether.

Limitations of our study included its single-center design and retrospective nature, with data obtained from patient records. Another significant limitation was the insufficient sample size.

Conclusion

In our study, we demonstrated that MS and BMI have negative effects on hematologic malignancies. We found that higher BMI is associated with refractory disease in the ALL group. Additionally, in the AML group, patients with MS had higher ECOG performance scores. In the DLBCL group, higher LDH levels were observed in the overweight subgroup, while absolute lymphocyte and white blood cell counts were higher in the underweight subgroup compared to other BMI groups. In the KML group, elevated basophil counts were noted in the overweight and obese subgroups, along with higher uric acid levels. Moreover, in the MM group, higher R-ISS scores were observed in the overweight and obese subgroups, along with a higher number of patients meeting 2 and 3 SLIM criteria. Furthermore, in the obese subgroup of MM patients, sedimentation rate was higher. In the MM group, patients with MS had higher ECOG performance scores.

Based on the results of our study, MS and BMI play important roles in the development of hematologic malignancies. Furthermore, the presence of MS and high BMI negatively affect the prognosis and treatment responses of patients. Therefore, the presence of MS and high BMI should be carefully investigated in patients with hematologic malignancies, and measures should be taken to prevent MS and high BMI.

REFERENCES

1. Cornier M-A, Dabelea D, Hernandez TL, et al. The metabolic syndrome. Endocr Rev 29: 777-822, 2008.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. The Lancet 365: 1415-1428, 2005.
3. Zimmet P, Alberti K, Shaw J. Global and societal implications of the diabetes epidemic. Nature 414: 782-787, 2001.
4. Braun S, Bitton-Worms K, LeRoith D. The link between the metabolic syndrome and cancer. Int J Biol Sci 7: 1003, 2011.
5. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 11: 886-895, 2011.
6. Kern PA, Ranganathan S, Li C, et al. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 280: E745-751, 2001.
7. Calado DP, Zhang B, Srinivasan L, et al. Constitutive canonical NF-κB activation cooperates with disruption of BLIMP1 in the pathogenesis of activated B cell-like diffuse large cell lymphoma. Cancer Cell 18: 580-589, 2010.
8. Danø K, Behrendt N, Høyer-Hansen G, et al. Plasminogen activation and cancer. J Thromb Haemost 93: 676-681, 2005.
9. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. The Lancet 375: 2267-2277, 2010.
10. Barone BB, Yeh H-C, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 300: 2754-2764, 2008.

11. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol 9: 1039-1047, 2008.
12. Nagel G, Stocks T, Späth D, et al. Metabolic factors and blood cancers among 578,000 adults in the metabolic syndrome and cancer project (Me-Can). Ann Hematol 91: 1519-1531, 2012.
13. Ju S-Y, Lee J-Y, Kim D-H. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-analysis of prospective cohort studies. Medicine 96: e8491, 2017.
14. Reaven G. Role of insulin resistance in human Samochowiec disease (syndrome X). Annu. Rev. Med. 44: 121-131, 1993.
15. Onat A, Yüksek H. Türk eriskinlerinde obezite ile abdominal obezite belirleyicileri ve sonuçlarÞ. Icinde: TEKHARF 2017. Onat A. Logos Yayincilik, Istanbul: 141-152, 2017.
16. Eckel RH. Obesity: Mechanisms and Clinical Management. Lippincott Williams & Wilkins Philadelphia, PA, 2003: 83-114.
17. Markus E, Trestman S, Cohen Y, et al. Components of metabolic syndrome in patients with multiple myeloma and smoldering multiple myeloma. BMC Cancer 20: 1-8, 2020.
18. Bromberg J, Wrzeszczynska M, Devgan G, et al. Stat3 as an Oncogene. Cell 98: 295-303, 1999.
19. Butturini AM, Dorey FJ, Lange BJ, et al. Obesity and outcome in pediatric acute lymphoblastic leukemia. J Clin Oncol 25: 2063-2069, 2007.
20. Papageorgiou SG, Kotsianidis I, Bouchla A, et al. Serum ferritin and ECOG performance status predict the response and improve the prognostic value of IPSS or IPSS-R in patients with high-risk myelodysplastic syndromes and oligoblastic acute myeloid leukemia treated with 5-azacytidine: a retrospective analysis of the Hellenic national registry of myelodysplastic and hypoplastic syndromes. Ther Adv Hematol 11: 2040620720966121, 2020.
21. Rabinovich E, Pradhan K, Sica RA, et al. Elevated LDH greater than 400 U/L portends poorer overall survival in diffuse large B-cell lymphoma patients treated with CD19 CAR-T cell therapy in a real world multi-ethnic cohort. Exp. hematol. Oncol. 10: 1-4, 2021.
22. Feng J, Wang Z, Guo X, et al. Prognostic significance of absolute lymphocyte count at diagnosis of diffuse large B-cell lymphoma: a meta-analysis. Int J Hematol 95: 143-148, 2012.
23. Han X, Ruan J, Zhang W, et al. Prognostic implication of leucocyte subpopulations in diffuse large B-cell lymphoma. Oncotarget 8: 47790, 2017.
24. Denburg JA, Browman G. Prognostic implications of basophil differentiation in chronic myeloid leukemia. Am J Hematol 27: 110-114, 1988.
25. Vonka V, Humlova Z, Klamova H, et al. Kynurenine and uric acid levels in chronic myeloid leukemia patients. Oncoimmunology 4: e992646, 2015.
26. Udupa CBK, Udupa KS, Pai A, Sherigar P. Cytogenetics and revised international staging system (R-iss): Risk stratification in multiple myeloma-a retrospective study in indian population. Iran J Pathol 15: 182, 2020.
27. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 33: 2863, 2015.
28. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15: e538-e548, 2014.
29. Alexandrakis M, Passam F, Ganotakis E, et al. The clinical and prognostic significance of erythrocyte sedimentation rate (ESR), serum interleukin-6 (IL-6) and acute phase protein levels in multiple myeloma. Clin lab Haematol 25: 41-46, 2003.
30. Afram G, Gran C, Borg Bruchfeld J, et al. Impact of performance status on overall survival in patients with relapsed and/or refractory multiple myeloma: Real-life outcomes of daratumumab treatment. Eur J Haematol 105: 196-202, 2020.
31. Topcu FB, Ozdemir S, Malkan UY. The relationship of vitamin D levels with hematological neoplasia. UHOD 33: 227-239, 2023.
32. Bennour I, Haroun N, Sicard F, et al. Vitamin D and obesity/adiposity- A brief overview of recent studies. Nutrients 14: 2049, 2022.

Correspondence:
Dr. Burak BIRSOY
Ankara Etlik State Hospital
Department of Gastroenterology
06170 Diskapi
ANKARA / TURKIYE

Tel: (+90-534) 228 32 17
e-mail: burak_birsoy@hotmail.com

ORCIDs:
Burak Birsoy 0000-0003-1052-9170
Umit Yavuz Malkan 0000-0001-5444-4895