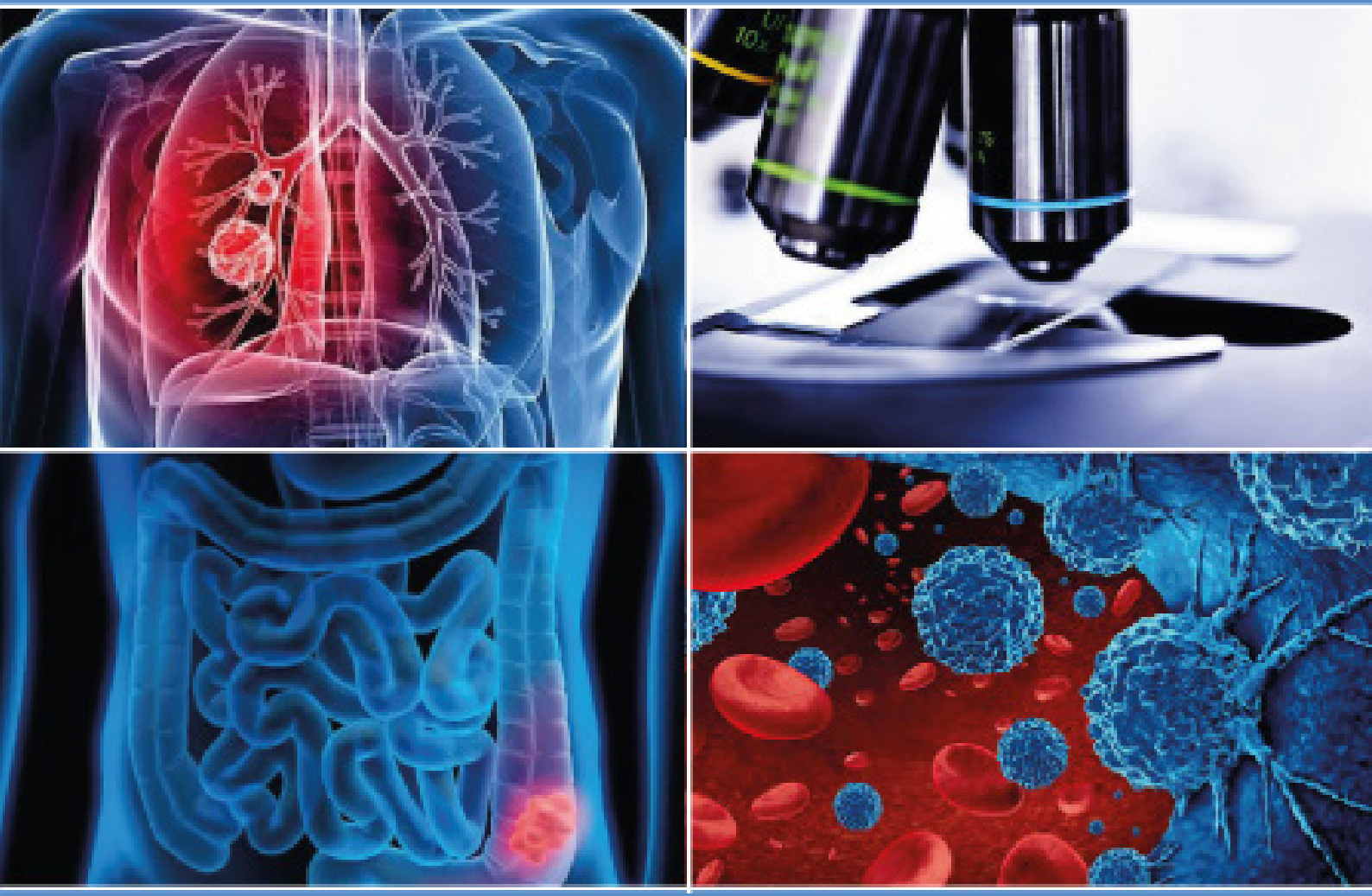
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Journal of Current Hematology & Oncology Research

Original Article

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Real-world outcomes for primary and secondary central nervous system lymphoma

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ABSTRACT

Aims: Central nervous system lymphoma (CNSL) is a rare and aggressive subtype of extranodal non-Hodgkin lymphoma, including primary and secondary forms. Despite advances in treatment, outcomes remain suboptimal. In this study, real-world treatment outcomes and prognostic factors in CNSL patients were evaluated.

Methods: We retrospectively analyzed 40 patients diagnosed with CNSL at Gazi University Hospital between 2003 and 2022. Clinical characteristics, treatment modalities, response rates, transplantation and survival outcomes were evaluated.

Results: The median age was 53 years, and 62.5% of patients had primary CNSL. High-dose methotrexate-based regimens yielded high response rates, with overall response rates (ORR) of 92.3% for the MATRix regimen and 86.7% for the modified Bonn protocol. Autologous stem cell transplantation (ASCT) was associated with an improvement in complete/unconfirmed complete response rates (67.8% pre-ASCT vs. 83.8% post-ASCT). At a median follow-up of 1124 days, the overall survival (OS) and progression-free survival rates were 52.5% and 35%, respectively. Relapse occurred in 50% of patients. Prognostic scoring systems demonstrated limited applicability due to missing data and the small sample size.

Conclusion: High-dose methotrexate-based regimens followed by ASCT remain effective in CNSL; however, relapse rates remain high. Improved prognostic models and novel therapies are needed.

Keywords: Central nervous system lymphoma, primary central nervous system lymphoma, methotrexate, autologous stem cell transplantation

INTRODUCTION

Central nervous system lymphoma (CNSL) is a rare, aggressive form of extranodal non-Hodgkin lymphoma that can develop as primary or secondary due to systemic disease.[1] Primary central nervous system lymphoma (PCNSL) is defined as the presence of disease in the brain, spinal cord, cranial nerves, leptomeninges or eyes without systemic lymphoma. Secondary central nervous system lymphoma (SCNSL) initially presents systemically and then relapses with central nervous system (CNS) involvement, or systemic and CNS involvement are seen simultaneously at diagnosis.[2,3] Although they are biologically different diseases, treatment approaches are similar in PCNSL and SCNSL. High-dose methotrexate-based multiagent chemotherapy protocols form the basis of induction therapy in CNSL. Autologous stem cell transplantation (ASCT) or radiotherapy is used in consolidation treatment.[4-6] Different prognostic scores are available for PCNSL, such as the International Extranodal Lymphoma Study Group (IELSG), Nottingham/Barcelona, Memorial Sloan Kettering Cancer Center and Taipei Score. Although the IELSG model was created based on a relatively large patient sample from multiple centers, it is not easy to use in daily practice, as information on cerebrospinal fluid protein is not available in many patients.[7]

In this retrospective study, we evaluated the treatment outcomes and prognostic factors in patients diagnosed with CNSL.

METHODS

Ethics

This study was approved by the Clinical Researches Ethics Committee of Gazi University (Date: 10.10.2022, Decision No: 730). All procedures were conducted in accordance with ethical guidelines and the principles of the Declaration of Helsinki.

Patients

A total of 40 patients diagnosed with CNSL at Gazi University Hospital between October 1, 2003 and September 27, 2022 were retrospectively reviewed. The pathology of all patients diagnosed with PCNSL and SCNSL in this study was diffuse large B-cell lymphoma.

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Response Assessment

Response assessment was performed using [18F] FDG-PET/CT and contrast-enhanced MRI according to the criteria of the International Primary CNS Lymphoma Collaborative Group.[8] Lugano response assessment criteria were also used for patients with concomitant systemic and CNS involvement.[9]

Chemotherapy Protocols

Treatment was administered according to time period-based standard treatment protocols recommended in the literature. Patients who received 3–4 cycles of the MATRix regimen were treated with a combination immunochemotherapy consisting of rituximab, high-dose methotrexate, cytarabine, and thiotepa, including leucovorin rescue therapy. In patients treated with the modified Bonn regimen, Bonn A consisted of high-dose methotrexate–based chemotherapy including vincristine, dexamethasone, and ifosfamide with mesna support; Bonn B consisted of high-dose methotrexate–based chemotherapy including vincristine, dexamethasone, and cyclophosphamide with mesna support, with leucovorin rescue administered in both; and Bonn C consisted of high-dose cytarabine with vincristine and dexamethasone.

Transplant Protocol

In patients undergoing ASCT for consolidation, the conditioning regimen consisted of thiotepa, cyclophosphamide, and busulfan. Hematopoietic stem cells were cryopreserved. Median infused CD34+ cell count was 5(2.92–9.07)×106/kg. All patients received 30 MIU filgrastim until neutrophil engraftment occurred on day +4th after transplantation.

Statistical Analysis

The primary endpoints of the study were overall response rate (ORR), progression free survival (PFS) rate and overall survival (OS) rate. Secondary endpoints were assessment of prognostic factors and autologous stem cell transplantation outcomes. Continuous variables were expressed as median/range and categorical variables as frequency/percentages using descriptive statistics. The Kaplan Meier test was used for survival analysis. SPSS 26.0 (IBM Corp, Armonk, NY, USA) program was used for statistical analysis.

RESULTS

A total of 40 patients were included in the study [median age: 53(27-77) years, male/female: 23(57.5%)/17(42.5%)]. Twenty-five patients (62.5%) had PCNSL, 8 patients (20%) had relapses with SCNSL, 7 patients (17.5%) had concomitant SCNSL. Of the 29 patients who underwent subtyping, 18 patients (62.1%) had a non-germinal center phenotype, 11 patients (37.9%) had a germinal center phenotype. No patient was found to be HIV positive; 2 patients (5%) had a history of renal transplantation. Hypogammaglobulinemia was observed in five of the 35 patients (14.3%). Seven patients (17.5%) had B-symptoms. The median IELSG score among patients with PCNSL was 2 (range: 0–5), and cerebrospinal fluid protein levels were available for inclusion in the IELSG score calculation in only 7 patients (28%). Of the 8 patients who did not have CNS involvement at diagnosis, 6 patients had a high CNS-IPI risk score and 2 patients had an intermediate CNS-IPI risk score. In these patients, relapses with CNS occurred after a median of 318 (180-887) days and 6 patients had not received prophylaxis against CNS relapse. The median number of chemotherapy lines was 2 (0-5) including ASCT. Seventeen patients (42.5%) received radiotherapy, of whom two were treated in the first-line setting. One patient underwent craniospinal irradiation, while the remaining patients received cranial radiotherapy (94.1%). Among the 13 patients evaluable for radiotherapy response, 5 (38.5%) achieved a partial response (PR), whereas 8 (61.5%) achieved a complete response or unconfirmed complete response (CR/CRu). The characteristics of the study population are summarized in **Table 1**, and the characteristics of patients with SCNSL are summarized in **Table 2**.

Table 1. Patient characteristics

Age, years, median (range)	53 (27-77)
Gender (male/female) [n (%)]	23 (57.5)/17 (42.5)
Disease [n (%)]	
Primary CNSL	25 (62.5)
Relapses with secondary CNSL	8 (20)
Concomitant secondary CNSL	7 (17.5)
ECOG status [n (%)]	
≤1	25 (62.5)
2	11 (27.5)
3	4 (10)
Serum LDH [n (%)]	
Normal	11 (28.9)
High	27 (71.1)
Involvement area [n (%)]	
Parenchymal	32 (80)
Leptomeningeal	1 (2.5)
Parenchymal & leptomeningeal	7 (17.5)
Deep brain involvement [n (%)]	
Yes	29 (72.5)
No	11 (27.5)
Follow up period, day, median (range)	1124 (18-7765)
Relapse pattern [n (%)]	
CNS only	18 (45)
CNS+systemic	2 (5)
Relapse time [n (%)]	
<1 year	12 (30)
1-2 years	5 (12.5)
>2 years	3 (7.5)
Mortality rate [n (%)]	19 (47.5)
Disease-related	14 (35)
Transplantation-related	3 (7.5)
Non-relapse	2 (5)
Progression-free survival rate [n (%)]	14 (35)
Overall survival rate [n (%)]	21 (52.5)

CNS: Central nervous system, CNSL: Central nervous system lymphoma, ECOG: Eastern Cooperative Oncology Group, LDH: lactate dehydrogenase, n: number

In the first-line treatment, 13 patients received the MATRix protocol, and 15 patients received the Modified Bonn protocol. The ORR was 92.3% in patients receiving MATRix therapy, whereas it was 86.7% in those receiving Modified Bonn chemotherapy (p=0.63). For patients receiving the Modified Bonn and MATRix protocols, the 2-year OS rates were 86% and 61% (log-rank p=0.33), while the 2-year PFS rates were 58% and 52% (log-rank p=0.82), respectively (**Figure 1A, 1B**).

ASCT was performed in 31 patients (77.5%). Among patients who underwent ASCT, response rates before transplantation were 67.8% for CR/CRu, 22.6% for PR, and 9.7% for PD. Following ASCT, the CR/CRu rate increased to 83.8%,

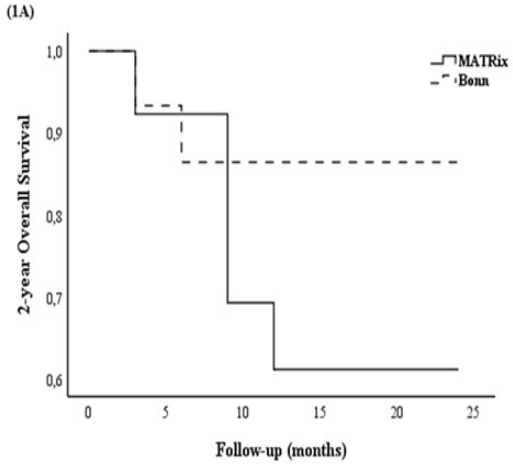
while the rates of PR and PD decreased to 6.5% and 3.2%, respectively. The characteristics of patients who underwent ASCT are presented in **Table 3**.

Table 2. Characteristics of patients with secondary central nervous system lymphoma

Ann Arbor stage at diagnosis [n (%)]	
Stage 2	1 (6.7)
Stage 3	2 (13.3)
Stage 4	12 (80)
Bulky mass [n (%)]	
Yes	3 (20)
No	12 (80)
Splenic involvement [n (%)]	
Yes	3 (20)
No	12 (80)
Bone marrow involvement [n (%)]	
Yes	1 (6.7)
No	14 (93.3)
Extranodal involvement [n (%)]	
0	3 (20)
1	2 (13.3)
≥2	10 (66.7)
International Prognostic Index [n (%)]	
2	5 (35.7)
3	4 (28.6)
4-5	5 (35.7)
Missing	1(6.7)

n: number

(A) Overall survival rate.



(B) Progression-free survival rate.

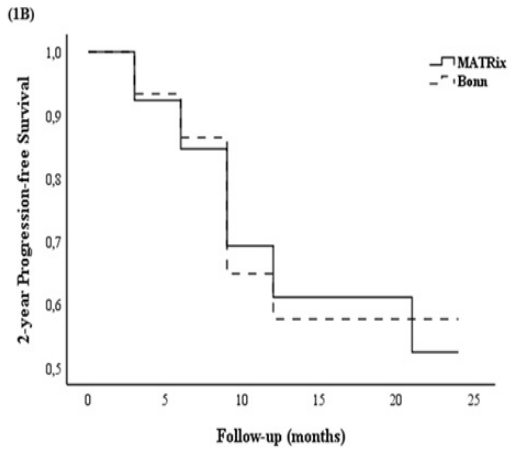


Figure 1. Estimated 2-year survival analysis comparing MATRix and modified Bonn protocols

Table 3. Transplantation characteristics

ASCT performed [n (%)]	
Yes	31 (77.5)
No	9 (22.5)
Pre-transplantation HCT-CI, median (range)	0 (0-7)
CD34+ cell count (×10⁶/kg), median (range)	5 (2.92–9.07)
Pre-transplantation disease status [n (%)]	
Complete response	11 (35.5)
Unconfirmed complete response	10 (32.3)
Partial response	7 (22.6)
Progressive disease	3 (9.7)
Post-transplantation disease status [n (%)]	
Complete response	25 (80.6)
Unconfirmed complete response	1 (3.2)
Partial response	2 (6.5)
Progressive disease	1 (3.2)
Death before response assessment	2 (6.5)

ASCT: Autologous stem cell transplantation, HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index, n: number

When patients with PCNSL were evaluated according to the Taipei score, 6 patients (24%) had a score of 0 and were classified as low risk, 11 patients (44%) had a score of 1 and were classified as intermediate risk, and 8 patients (32%) had a score of 2 and were classified as high risk. Due to the small sample size, survival analysis was performed by grouping patients into two categories: low risk and intermediate–high risk. OS was 66.7% in the low-risk group and 47.4% in the intermediate–high-risk group; however, this difference was not statistically significant (p=0.34). PFS was 66.7% in the low-risk group and 42.1% in the intermediate–high-risk group, and this difference was also not statistically significant (p=0.27). The laboratory findings at diagnosis are presented in **Table 4**.

Table 4. Laboratory findings of patients

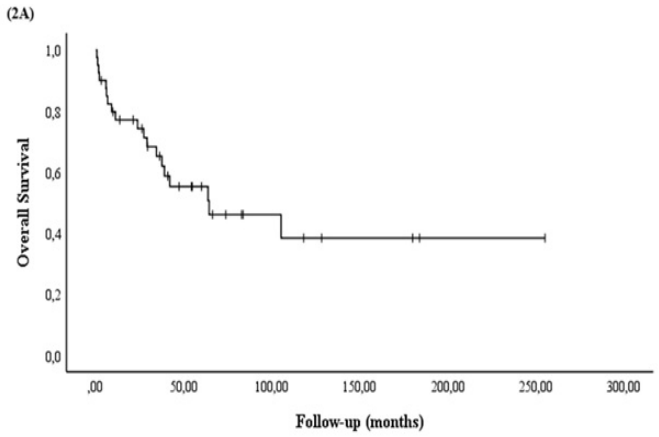
Hemoglobin (g/dl), median (range)	13.2 (8.1-17.1)
Leukocyte count (/μL), median (range)	9250 (3720-18180)
Lymphocyte count (/μL), median (range)	1400 (130-4980)
Lactate dehydrogenase level (U/L), median (range)	315 (168-1916)
Albumin (g/dl), median (range)	3.9 (2.2-5.1)

At a median follow-up of 1124 days (18–7765), the OS rate was 52.5% and the PFS rate was 35% (**Figure 2A, 2B**). Twenty patients (50%) experienced relapse, with a median of 1 relapse (1–4). The median PFS was 363.5 days (18–5476), and the median OS after CNS involvement was 1117 days (18–7378).

DISCUSSION

High-dose methotrexate-based multiagent chemotherapy constitutes the backbone of induction therapy in CNSL; however, no universally accepted standard regimen exists. In this context, we aimed to evaluate treatment outcomes across different therapeutic approaches. Additionally, both ASCT and radiotherapy are utilized in consolidation, ASCT has increasingly become the preferred strategy, and we therefore specifically analyzed transplantation outcomes in our study. Given the limited availability of cerebrospinal fluid protein measurements, which are required for the IELSG score, we employed the Taipei score as a more feasible tool for prognostic assessment in patients with PCNSL in this retrospective single-center study.

(A) Overall survival rate.



(B) Progression-free survival rate

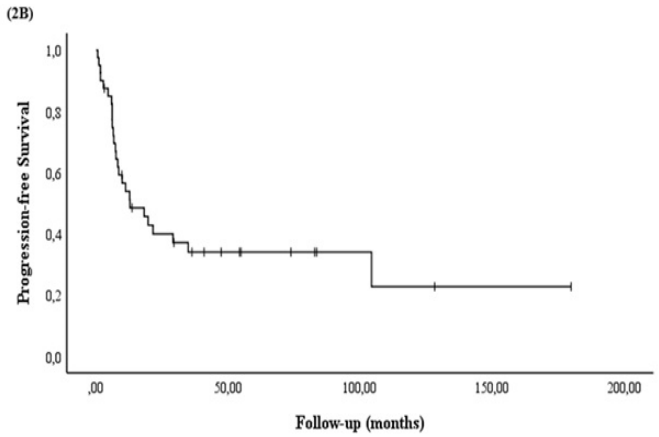


Figure 2. Survival analysis

Although ORR was high in both the MATRix and modified Bonn regimen groups, no statistically significant difference was observed between the two regimens (92.3% vs. 86.7%, p=0.63). Among patients treated with the MATRix and Modified Bonn regimen protocols, the 2-year OS rates were 61% and 86% (log-rank p=0.33), respectively, while the corresponding 2-year PFS rates were 52% and 58% (log-rank p=0.82). This lack of statistical significance in OS may be related to the limited sample size. However, despite the favorable ORR, survival outcomes remained comparatively modest. In the IELSG32 study,[10] among patients treated with the MATRix regimen and consolidated with radiotherapy or ASCT, the 4-year OS rates were 85% and 83%, respectively (p=0.39). Zeyen et al.[11] reported 2-year PFS and 5-year OS rates of 56% and 76%, respectively, in patients receiving the modified Bonn regimen. The poorer survival outcomes in the MATRix group may be explained by the inclusion of patients with SCNSL and the limited sample size in our study. [10,11]

In our study, CR/CRu rates increased from 67.8% prior to ASCT to 83.8% after transplantation. This finding is consistent with existing evidence supporting ASCT as a consolidation strategy in patients with CNSL. Recent studies have demonstrated that ASCT following thiotepa-based conditioning regimens is associated with improved PFS and OS, particularly in patients who achieve a response to induction chemotherapy.[12,13]

The role of radiotherapy in CNSL continues to evolve. In our study, radiotherapy proved effective as a salvage or consolidation modality, achieving high complete response rates among evaluable patients. However, concerns regarding neurotoxicity and quality of life are increasing. Recent studies have increasingly shifted radiotherapy to a less prominent role, particularly in younger and transplant-eligible patients.[14]

Despite these encouraging response rates, disease relapse remains a major clinical challenge. In line with previous reports, relapse was observed in 50% of patients in our cohort, even with intensive induction and consolidation approaches.[15,16] Despite the use of high-dose methotrexate-based induction regimens followed by consolidation with ASCT, relapse rates remain substantial, thereby necessitating the development of novel therapeutic approaches. Phase I/II trials evaluating targeted agents such as ibrutinib and lenalidomide in induction therapy are ongoing, with long-term outcomes awaited.[6,17] Immune checkpoint inhibitors and CAR-T cell therapies represent emerging options, particularly in heavily pretreated patients. PD-1/PD-L1 blockade has shown potential clinical benefit in CNS lymphomas, suggesting a role in overcoming immune evasion.[18,19] Additionally, tirabrutinib monotherapy has demonstrated encouraging activity in relapsed disease in phase I/II studies.[20, 21]

Limitations

Our analysis of prognostic scoring systems underscores notable limitations in their applicability to routine clinical practice. Despite its extensive validation, the IELSG score could not be fully calculated in the majority of our cohort due to the unavailability of cerebrospinal fluid protein data. This previously acknowledged constraint highlights the necessity for more pragmatic and readily implementable prognostic models. Although the Taipei score, proposed as a simplified alternative, demonstrated a capacity to stratify patients into distinct risk groups within our cohort, this differentiation did not achieve statistical significance, likely attributable to the limited sample size.[7]

The limitations of this study include its retrospective design, the small sample size, and the heterogeneous patient population. Further prospective randomized controlled trials with larger, more homogeneous cohorts are warranted.

CONCLUSION

Our findings support the continued use of high-dose methotrexate-based induction regimens followed by ASCT consolidation in eligible patients with CNSL. While high response rates can be achieved, relapses remain a major obstacle, highlighting the need for improved risk stratification and incorporation of novel therapeutic strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of Gazi University (Date: 10.10.2022, Decision No: 730).

Informed Consent
This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process
This manuscript was subject to external peer review.

Conflict of Interest
The authors declare no conflicts of interest related to this study.

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Association between the CALLY index and thrombotic risk in polycythemia vera and essential thrombocythemia

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ABSTRACT

Aims: Thrombotic complications are the leading cause of morbidity and mortality in patients with polycythemia vera (PV) and essential thrombocythemia (ET). The C-reactive protein–albumin–lymphocyte (CALLY) index has recently emerged as a biomarker reflecting systemic inflammation, nutritional status, and immune function. This study aimed to evaluate the association between the CALLY index and thrombotic risk in patients with PV and ET.

Methods: This retrospective single-center study included 96 adult patients diagnosed with PV or ET between 2015 and 2026. Clinical and laboratory data were obtained from hospital records. Thrombotic events present at diagnosis were confirmed using imaging methods. Receiver operating characteristic (ROC) analysis was performed to evaluate the discriminative ability of the CALLY index, and multivariate logistic regression analysis was used to identify independent factors associated with thrombosis.

Results: Among the patients, 77 (80.2%) had PV and 19 (19.8%) had ET. Thrombosis was detected in 27 patients. Patients with thrombosis had significantly lower CALLY scores compared to those without thrombosis (11.8±10.4 vs 19.2±18.9, p=0.010). Neutrophil counts were significantly higher in the thrombosis group (p=0.014). Lymphocyte counts were significantly lower in patients with thrombosis compared to those without thrombosis (p=0.016). ROC analysis demonstrated moderate discriminative ability for thrombosis (AUC: 0.670, 95% confidence interval (CI): 0.543–0.788). In multivariate analysis, a low CALLY index (<12) was independently associated with thrombosis (odds ratio (OR): 4.33, 95% CI: 1.54–12.15, p=0.015).

Conclusion: The lower CALLY index may represent a simple and clinically supportive biomarker for thrombotic risk assessment in PV and ET patients.

Keywords: Biomarkers, essential thrombocythemia, polycythemia vera, thrombosis

INTRODUCTION

Polycythemia vera (PV) and essential thrombocythemia (ET) are classic myeloproliferative neoplasms (MPNs) with the potential to progress to myelofibrosis or acute leukemia.[1] Across this disease spectrum, thromboembolic complications stand out as the foremost contributor to morbidity and death.[2] In recent years, the C-reactive protein–albumin–lymphocyte (CALLY) index—a single metric that captures systemic inflammation, nutritional state, and host immunity—has attracted growing interest as a practical, low-cost laboratory tool.[3,4]

The CALLY index integrates C-reaktif protein (CRP) as a marker of inflammation, albumin as an indicator of nutritional status, and lymphocyte count as a key component of immune function into a single scoring system.[5] This index has been shown to serve as an important prognostic value not only in various oncological conditions, including colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, and esophageal cancer, but also in cardiovascular diseases.[6–9]

Among hematologic malignancies, recent studies—particularly in primary myelofibrosis (PMF)—have demonstrated that the CALLY index may have prognostic potential in specific clinical subgroups of patients with prior thrombosis.[10] Yet whether this index meaningfully stratifies thrombotic risk in PV and ET has not been adequately addressed. Therefore, the aim of the present study is to evaluate the association between the CALLY index at diagnosis and vascular complications in PV and ET patients.

METHODS

This study was approved by the Non-interventional Clinical Researches Ethics Committee of Kütahya Health Sciences University (Date: 09.03.2026, Decision No: 2026/03-43). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Designed as a single-center retrospective observational study, this research enrolled adult patients diagnosed with

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PV or ET at the Kütahya Health Sciences University Kütahya City Hospital's Hematology Clinic between January 2015 to February 2026. Demographic characteristics, clinical findings, and laboratory parameters were recorded for all patients from patient files and hospital information systems. Baseline CALLY scores were derived from laboratory values obtained at the time of diagnosis using the formula below.[11]

CALLY index=albumin level (g/dl)×lymphocyte count (/μL)/ CRP level (mg/dl)x10^4

As laboratory parameters in our institution are routinely reported in SI units, the formula was adapted accordingly as: CALLY index=Albumin (g/L)×Lymphocyte count (×10^9/L)/ CRP (mg/L). The criteria for thrombotic events included arterial or venous thrombosis located in the cerebral, coronary, pulmonary, abdominal, or peripheral vascular systems. All events required radiological confirmation via computed tomography (CT), magnetic resonance imaging (MRI), or Doppler ultrasonography.

Statistical Analysis

All analyses were conducted with IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean±standard deviation and categorical variables as frequencies with percentages. Group comparisons for continuous measures used the Mann–Whitney U test, selected on the basis of distributional properties; categorical variables were compared with the chi-square test. The ability of the CALLY index to discriminate thrombosis was evaluated using ROC curve analysis. To identify independent risk factors, we built a multivariate logistic regression model incorporating variables that reached p<0.05 in univariate testing. A two-tailed p value below 0.05 was considered statistically significant throughout.

Table 1. Demographics and clinical characteristics of patients(n=96)

Variables	All patients (n=96), %
Gender, male (%)	60 (62.5)
PV	77 (80.2)
ET	19 (19.8)
JAK2 V617F (+)	82 (85.4)
Splenomegaly (+)	47 (49.0)
B symptoms (+)	22 (22.9)
ECOG 0	62 (64.6)
ECOG 1	24 (25.0)
ECOG 2	7 (7.3)
ECOG 3	3 (3.1)
Myelofibrotic Transformation	8 (8.3)
Survival, exitus	1 (1.0)
	Mean±SD
Age (year)	62.1±14.5
Albumin (g/L)	44.2±2.7
Hgb (g/dl)	16.9±1.8
Hct (%)	50.2±6.5
WBC (×10^9/L)	11.2±4.2
Neutrophil count (×10^9/L)	7.8±3.6
Lymphocyte count (×10^9/L)	2.3±0.8
Monocyte (×10^9/L)	0.7±0.4
Platelet (×10^9/L)	516±284
MPV	9.9±1.1
LDH	251.2±78.4
CRP (mg/L)	9.47±7.01
CALLY index	12.6±18.5

PV: Polycythemia vera, ET: Essential thrombocythemia, JAK2 V617F: Janus kinase 2 V617F mutation, ECOG: Eastern Cooperative Oncology Group, SD: Standard deviation, Hct: Hematocrit, Hgb: Hemoglobin, WBC: White blood cell, MPV: Mean platelet volume, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CALLY: C-reactive protein-Albumin-Lymphocyte index

RESULTS

Ninety-six patients with PV or ET formed the study population. Males predominated (62.5%), and diagnosed with PV (80.2%), while 19.8% had ET. The Janus kinase 2 V617F mutation (JAK2 V617F) mutation was present in 85.4% of patients. Splenomegaly and B symptoms were observed in 49.0% and 22.9% of patients, respectively. Performance status was generally preserved, with 64.6% achieving Eastern Cooperative Oncology Group (ECOG) 0. During follow-up, myelofibrotic transformation occurred in 8.3% of patients, while only one death (1.0%) was recorded. The mean age of the patients was 62.1±14.5 years. Laboratory parameters were consistent with the underlying myeloproliferative phenotype, with elevated hemoglobin, hematocrit, and platelet levels. The mean CALLY index was 12.6±18.5 (**Table 1**). The median follow-up duration was 36 months (range, 10–125 months).

Thrombosis was documented in 27 patients (29%), occurring either at diagnosis (n=8) or following diagnosis (n=19). Arterial thrombosis was observed in 20 patients, including coronary artery thrombosis in 14, cerebrovascular events in 5, and peripheral artery thrombosis in 1. Venous thrombosis was present in 7 patients, comprising deep vein thrombosis in 5, pulmonary embolism in 1, and superficial thrombophlebitis in 1. Comparing the two groups, we found no meaningful differences in age, gender, diagnosis subtype, splenomegaly, B symptoms, ECOG score, JAK2 status, or myelofibrotic transformation (all p>0.05). On the laboratory side, neutrophil count stood out as significantly elevated in thrombotic patients (8.9±3.4 vs 7.5±3.6×10^9/L, p=0.014), while lymphocyte counts were lower in this group (p=0.016). Other hematologic variables, including hemoglobin, hematocrit, white blood cell count, monocyte count, mean platelet volume (MPV), and lactate dehydrogenase (LDH), were comparable between the groups. Importantly, the CALLY index was significantly lower among thrombotic patients (11.8±10.4 vs 19.2±18.9, p=0.010), suggesting an inverse relationship between CALLY levels and thrombotic risk (**Table 2**).

ROC analysis demonstrated that the CALLY index had a modest discriminative ability in identifying thrombosis, with an area under the curve (AUC) of 0.670 (95% confidence interval (CI): 0.543–0.788). The optimal cut-off value was identified as 12.0 using the Youden index, yielding a sensitivity of 74.1% and a specificity of 62.3% (**Figure**).

Variables that were significantly associated with thrombosis in univariate analyses, including the CALLY index (<12) and neutrophil and lymphocyte count, were subsequently included in a multivariate analysis. Multivariate modeling showed that patients with a CALLY index <12 had a significantly higher risk of thrombosis (odds ratio (OR): 4.33, 95% CI: 1.54–12.15, p=0.015). Although neutrophil and

Table 2. Comparison of clinical, hematologic, and inflammatory indices between patients with and without thrombosis

Variable	Thrombosis (+) n=27	Thrombosis (-) n=69	p value
Age (year)	63.5±13.5	61.3±15.0	0.496
Albumin (g/L)	44.0±3.1	44.3±2.5	0.793
Hgb (g/dl)	17.3±1.0	16.7±2.1	0.367
Hct (%)	51.1±6.7	49.8±6.4	0.249
WBC ($\times10^9$/L)	11.6±3.7	11.0±4.4	0.357
Neutrophil count ($\times10^9$/L)	8.9±3.4	7.5±3.6	0.014
Lymphocyte count ($\times10^9$/L)	2.2±0.8	2.5±0.7	0.016
Monocyte ($\times10^9$/L)	0.7±0.6	0.7±0.3	0.257
MPV	10.0±1.3	9.8±1.0	0.607
LDH	254.3±77.9	250.0±79.1	0.867
CRP (mg/L)	8.81±6.83	9.44±5.77	0.650
CALLY index	11.8±10.4	19.2±18.9	0.010
ECOG 0	17 (63.0)	45 (65.2)	0.854
ECOG 1	7 (25.9)	17 (24.6)	0.901
ECOG 2	3 (11.1)	4 (5.8)	0.643
ECOG 3	0 (0.0)	3 (4.3)	0.654
JAK2 V617F (+)	25 (92.6)	57 (82.6)	0.223
Myelofibrotic Transformation	4 (14.8)	4 (5.8)	0.305
Splenomegaly (+)	15 (55.6)	32 (46.4)	0.592
B symptoms (+)	9 (33.3)	13 (18.8)	0.184
Death	1 (3.7)	0 (0.0)	0.625

Hgb: Hemoglobin, Hct: Hematocrit, WBC: White blood cell, MPV: Mean platelet volume, LDH: Lactate dehydrogenase, C-reactive protein, CALLY: C-reactive protein–albumin–lymphocyte index, ECOG: Eastern Cooperative Oncology Group, JAK2 V617F: Janus kinase 2 V617F mutation

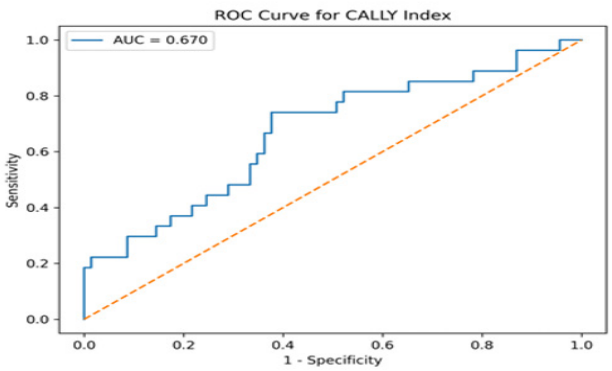


Figure. ROC curve analysis for thrombosis discrimination using the CALLY index. The area under the curve was 0.670 (95% CI, 0.543–0.788), and the optimal cut-off value determined by the Youden index was 12.0, with a sensitivity of 74.1% and a specificity of 62.3%.

lymphocyte counts did not retain independent statistical significance, the associations between neutrophils and thrombosis remained notable (**Table 3**).

Table 3. Multivariate logistic regression analysis for thrombosis

Variable	OR	95% CI	p value
CALLY <12	4.33	1.54 – 12.15	0.015
Neutrophil	1.12	0.99 – 1.28	0.069
Lymphocyte	1.36	0.75 – 2.46	0.312
		Nagelkerke R^2 = 0.165	

OR: Odds ratio, CI: Confidence interval, CALLY: C-reactive protein–albumin–lymphocyte index

DISCUSSION

This study evaluated the association between the CALLY index and the occurrence of thrombotic complications in cohorts of PV and ET patients. We found that a low CALLY index (<12) was associated with a substantially higher risk of thrombosis and remained an independent risk factor in this patient population. Given the multifactorial nature of thrombogenesis in myeloproliferative neoplasms, our results support the potential utility of composite biomarkers such as the CALLY index in improving risk stratification and identifying patients at higher risk for vascular complications.

Thrombosis drives much of the morbidity and mortality burden in PV and ET. While traditional risk stratification systems rely primarily on age and thrombosis history, increasing evidence suggests that chronic inflammation and immune dysregulation play central roles in MPN-associated thrombogenesis.[12] Inflammatory cytokine release promotes vascular events by contributing to endothelial dysfunction, platelet activation, leukocyte adhesion, and hypercoagulation. Recent studies have highlighted thromboinflammation as a feature of MPN biology and may represent a significant therapeutic target.[13,14]

The CALLY index combines CRP, albumin, and lymphocyte count in a single biomarker reflecting systemic inflammation, nutritional status, and host immune capacity.[15,16] Therefore, a low CALLY score may indicate a pro-inflammatory and immunologically disrupted microenvironment that supports the development of thrombosis. In our cohort, patients with thrombosis had significantly lower CALLY scores than those without thrombosis, supporting the hypothesis that inflammatory and immune-mediated mechanisms significantly contribute to vascular complications in PV and ET.

Other inflammation-based composite indices—the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and HALP score—have each been linked to thrombosis and poor outcomes in MPN populations.[17-19] Similar to these indices, the CALLY index appears to capture multiple biological pathways simultaneously. Importantly, unlike isolated inflammatory markers, the CALLY index combines inflammatory, nutritional, and immune parameters, potentially enhancing its prognostic utility in chronic inflammatory malignancies such as MPNs.

Another important finding of our study is the association between high neutrophil count and thrombosis. Although the neutrophil count did not retain statistical significance in the multivariate analysis, neutrophils are increasingly recognized as active mediators of thrombosis. This involvement is primarily driven by the formation of neutrophil extracellular traps (NETs), endothelial activation, and complex interactions with platelets. Experimental and translational studies have shown increased NETosis in MPN patients, particularly in JAK2 mutation disease, supporting the mechanistic role of neutrophils in MPN-associated thrombosis.[20-22]

ROC analysis showed that the CALLY index has moderate discriminatory performance in thrombotic risk, with an AUC of 0.670. Although this discriminative ability is modest, its relatively high sensitivity suggests that the CALLY index

could be used as a practical biomarker in daily clinical practice. Since CRP, albumin, and lymphocyte counts are routinely obtainable laboratory parameters, the CALLY index can be easily calculated without additional cost or the need for specialized testing. Nevertheless, the cut-off value of 12.0 identified in the present study was derived from a single-center retrospective cohort with a relatively small sample size, and its performance may not be generalizable to other populations. Therefore, this cut-off should be regarded as exploratory, and prospective, multicenter studies with external validation are needed before it can be recommended for routine clinical decision-making.

Limitations

This study has several limitations. First, the retrospective, single-center design may lead to selection bias. The relatively small sample size may have limited statistical power and prevented the detection of weaker associations. The limited number of ET patients and associated thrombotic events precluded a separate subgroup analysis due to the risk of statistical insufficiency and unreliable estimates. Consequently, our findings predominantly reflect the PV population, and their generalizability to ET patients is limited. In the present study, we used a multivariate logistic regression model including variables associated with thrombosis in univariate analysis, while also considering the limited number of thrombotic events to avoid model overfitting. Since lymphocyte count is a component of the CALLY index, the simultaneous inclusion of both variables in the multivariable model raises the possibility of multicollinearity, which could inflate the variance of the regression estimates and affect the stability of the odds ratios obtained. Due to data unavailability, known risk factors for PV and ET, such as cardiovascular risk factors (e.g., smoking, hypertension, diabetes mellitus, hyperlipidemia), treatment status, and hematocrit control, could not be evaluated. Arterial and venous thrombotic events were not analyzed separately. Additionally, thrombotic events present at diagnosis and those occurring during follow-up were analyzed together. Although all events were objectively confirmed, this approach may have introduced clinical heterogeneity because baseline and incident thrombotic events may reflect different underlying disease characteristics and risk profiles. Finally, the CALLY was assessed based on a single measurement at diagnosis; dynamic changes were not monitored.

CONCLUSION

Our findings demonstrate that a low CALLY index is independently associated with increased thrombotic risk in PV and ET patients. The CALLY index could be a simple, inexpensive, and clinically supportive biomarker reflecting the underlying inflammatory and immune mechanisms of thrombosis in MPNs. Furthermore, future prospective studies involving larger and more balanced PV and ET patient cohorts are needed to confirm the association separately for each disease subtype.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Clinical Researches Ethics Committee of Kütahya Health Sciences University (Date: 09.03.2026, Decision No: 2026/03-43).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: CY; Design: CY; Control: CÖ; Resources: CÖ, CY; Materials: CY, CÖ; Data Collection and/or Processing: CY, CÖ; Analysis and/or Interpretation: CÖ, CY; Literature Review: CÖ; Writing The Article: CY; Critical Review: CY, CÖ.

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Original Article

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Clinical features and management outcomes of hairy cell leukemia in routine clinical practice: a single center retrospective experience

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ABSTRACT

Aims: This study aimed to evaluate the clinical features and treatment outcomes of patients with classic hairy cell leukemia (HCL) in routine clinical practice.

Methods: This is a single-center retrospective study conducted at University of Health Sciences, Adana City Hospital, Hematology Department between January 2018 and August 2025. The data of 33 patients with the diagnosis of classic HCL from the database of hospital records were analysed.

Results: First line treatment was cladribine in 27 (81.8%) patients, rituximab-cladribine in 2 (6.1%) patients, interferon in 1 (3%) patient and splenectomy in 3 (9.1%) patients. Thirty one (93.9%) patients responded to treatment and only 2 (6.1%) did not. The progression was observed in 8 (25.8%) of 31 responding patients. The probablity of progression free survival (PFS) at 10 years was 33%. When the data is analysed according to the age groups of <50 y, 50-60 y and >60 y, the probability of PFS was 42.9%, 83.3%, 31.3%, respectively (p=0.096). Also patients were grouped according to the age ≤60 y and >60 y; and the probability of PFS at 10 years were 40.8% v.s 31.3% (p=0.034). All patients were alive at the end of follow up period, so median OS was not reached.

Conclusion: Cladribin was verified to be an effective treatment modality in HCL with high response rate, but low PFS. And the differences in the PFS according to age groups should be reevalated in the era of rituximab-cladribine combination and novel agents.

Keywords: Hairy cell leukemia, purine nucleoside analogs, cladribine, rituximab, prognosis

INTRODUCTION

Hairy cell leukemia (HCL) is an indolent B lymphoid malignancy classified under the splenic B cell lymphoma/leukemias in the last World Health Organization (WHO) classification 2022, and also in the International Consensus Classification (ICC). While HCL variant (HCLv) is among the subgroups of splenic B-cell lymphoma/leukemias with prominent nucleoli in WHO 2022 classification, it is a distinct entity as provisional under the splenic B-cell lymphoma/leukemias in ICC.[1,2] The classic and variant forms of HCL are considered separately, because the biological and clinical presentation of HCLv are quite different. Basically, BRAF mutation, a hallmark of HCL, is unavailable in HCLv, and HCLv is more aggressive and resistant to the conventional treatment compared to the classical variant.[1-3]

The accumulation of the mature-sized mature lymphocytes with hairy projections in the bone marrow, spleen and rarely extramedullary tissues, is the characteristic of HCL.[2-4] Although fatique and infection are encountered frequently at presentation of HCL, with the widespread health screenings mild pancytopenia has also emerged as an initial finding.[3,5] A trephine bone marrow biopsy examination is fundamental in the diagnosis of HCL.[2-5] Due to the indolent nature of the disease, patients with symptoms especially related to splenomegaly and with impaired hematological parameters that are either hemoglobin <11 g/dl or platelet count <100 000/µL or absolute neutrophil count <1000 µL should be treated.[2-4] The purine nucleoside analogs (PNAs) cladribine and pentostatin with rituximab constitutes first line treatment of HCL in recent years.[2-5] And novel agents such as vemurafenib, moxetumomab pasudotox, venetoclax and ibrutinib have come to use in relapse/refractory HCL patients.[2,4,5]

In this study, we aimed to review the clinical and treatment characteristics of classic HCL patients in the era of new developments in HCL.

METHODS

This study was approved by the Scientific Researches Ethics Committee of Adana City Training and Research Hospital

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(Date: 15.01.2026, Decision No: 983). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a single-center retrospective study conducted at University of Health Sciences, Adana City Hospital, Hematology Department between January 2018 and August 2025. We evaluated the data of 40 patients with the diagnosis of classic HCL from the database of hospital records and included the patients who had adequate information about the diagnosis, past history and follow-up. So, the data of 33 patients were analysed. The data comprising age, gender, disease and treatment characteristics were recorded from the database of the hospital records.

We aimed to use response criteria according to Consensus Resolution.[3] However all the patients did not have bone marrow biopsy after the treatment. So we evaluated peripheral blood counts, and spleen size and when the patient fulfilled the criteria of at least partial response, it was accepted as response. The progression free survival was defined as the length of time from the date of treatment to the date of progression. The age groups were determined considering the age distribution of the cohort.

Statistical Analysis

The data evaluation was made by IBM SPSS Statistics (version 24.0; IBM Corp., Armonk, NY, USA). Data were described as numbers and percentage or median and range, when appropriate. Kaplan-Meier and Cox regression survival analysis were used for survival analysis. The reverse Kaplan-Meier analysis was used for calculation of median follow-up duration. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

RESULTS

The clinical data of 33 patients is presented in Table 1. The median age of the patients at the time of diagnosis was 52 y (range, 33-76). Ten (30.3%) patients were female and 23 (69.7%) were male. The symptoms of the patients prior to the diagnosis were fatigue in 10 (30.2%) patients, bleeding in 2 (6.1%) patients, abdominal pain in 9 (27.3%) patients, flu-like symptoms in 2 (6.1%) patients, fever in 1 (3%) patient and 9 (27.3%) patients had no symptoms who were diagnosed due to abnormal complete blood counts during their rutin evaluation. The median hemoglobin was 9.7 g/dl (range, 6.5-15), white blood cell count was 2400x10^3/mm^3 (600-10700), neutrophil count was 560x10^3/mm^3 (range, 100-2800), monocyte count 100x10^3/mm^3 (range, 0-2300). Thirty-two (97%) patients had splenomegaly and 6 (18.2%) patients underwent splenectomy. The indication for treatment was constitutional symptoms in 11 (33.3%) patients, massive splenomegaly in 5 (15.1%) patients, anemia in 16 (48.5%) patients, thromboctopenia in 1 (3.1%), patient.

First line treatment was cladribine in 27 (81.8%) patients, rituximab-cladribin in 2 (6.1%) patients, interferon in 1 (3%) patient and splenectomy in 3 (9.1%) patients. The reason for splenectomy in 3 patients were; severe abdominal discomfort and massive splenomegaly in 2 patients and diagnostic purpose in 1 patient. Thirty one (93.9%) patients responded to the treatment and only 2 (6.1%) did not (Table 2). Those

Table 1. The patient characteristics

Characteristics	No of patients (%)
Total	33
Age, year (range)	52 (33-76)
Age range, n (%)	
<50	14 (42.4%)
50-60	9 (27.3%)
>60	10 (30.3%)
Gender (F/M)	10/23
Complaint of admission, n (%)	
B symptom	10 (30.2)
Abdominal pain	9 (27.3)
Bleeding	2 (6.1)
Flu-like symptoms	2 (6.1)
Fever	1 (3)
No symptom	9 (27.3)
Hemoglobin, g/dl (range)	9.7 (6.5-15)
White blood cell count, x10^3/mm^3, (range)	2400 (600-10700)
Neutrophil count, x10^3/mm^3, (range)	560 (100-2800)
Monocyte count, x10^3/mm^3, (range)	100 (0-2300)
Splenomegaly, n (%)	
Present	32 (97)
Splenectomy, n (%)	
Present	6 (18.2)

F: Female, M: Male

Table 2. The treatment characteristics

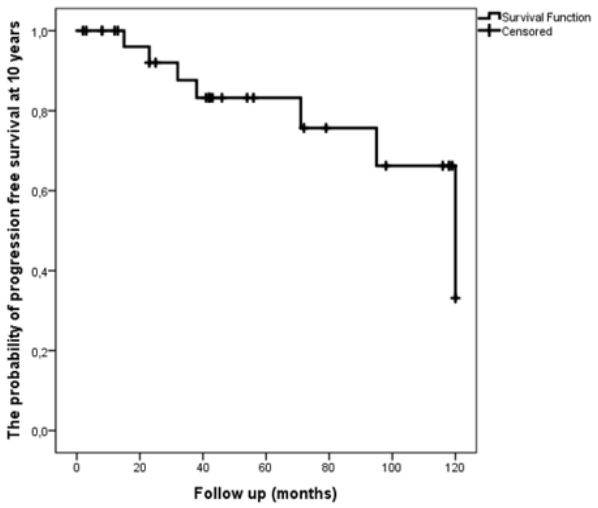
	n=33
First-line treatment, n (%)	
Cladribine	27 (81.8)
R-cladribin	2 (6.1)
Interferon	1 (3)
Only Splenectomy	3 (9.1)
Response to the first line treatment, n (%)	
Response	31 (93.9)
Non-response	2 (6.1)
Progression after first line treatment, n (%)	
Present	8 (25.8)
Absent	23 (74.2)
Second line treatment, n (%)	
Rituximab	2 (20)
Cladribin	1 (10)
R-cladribin	4 (40)
No treatment	3 (30)

R-cladribine: Rituximab-cladribine

2 patients had been treated with cladribine. One of the non-responding patient had massive splenomegaly with the size of 32 cm. He underwent splenectomy followed by rituximab-cladribine treatment. And he is now in complete remission. The other patient was retreated with only rituximab and partial reponse was obtained

The median follow-up duration was 43 months. The progression was observed in 8 (25.8%) of 31 responding patients. Seven patients who progressed after the first line treatment, had been treated with cladribine and 1 had been treated with only splenectomy in the first line. After prgression; 3 patients did not get second line treatment voluntarily, 2 (20%) patients were applied only rituximab, 1 (10%) patient was applied cladribine, and 4 (40%) patients were applied rituximab-cladribine (Table 2). The probability of progression free survival (PFS) at 10 years was 33% (95% CI:119 (76.7-161.2)) (Figure 1). When the data is analysed according to the age groups of <50 y, 50-60 y and >60 y, the probability of PFS was 42.9%, 83.3%, 31.3%, respectively (p=0.096) (Figure 2). Also the patients were grouped

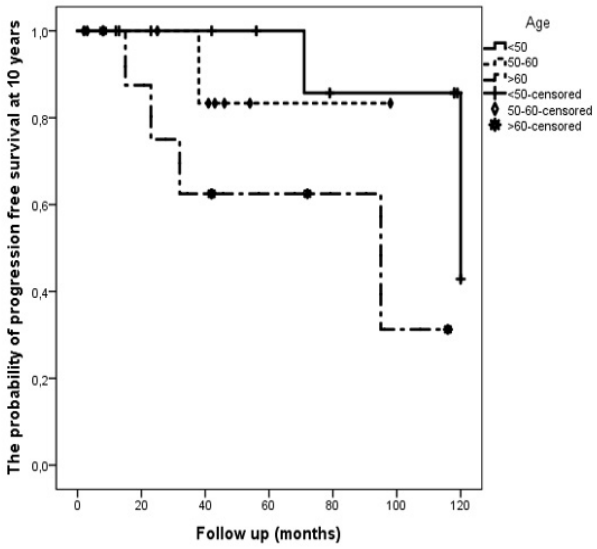
according to the age ≤60 y and >60 y; and the probability of PFS at 10 years were 40.8% v.s 31.3% (p=0.034) (**Figure 3**). The univariate analysis of the effect of age on PFS was not significant (p=0.057, OR: 0.192, 95% CI, 0.035-1.050) All the patients were alive at the end of follow up period, so median OS was not reached.



Number at risk

	31	24	19	11	8	6	2
	0	20	40	60	80	100	120

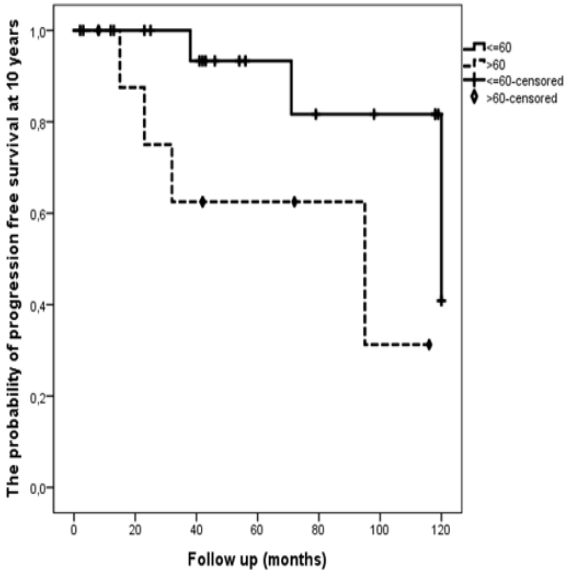
Figure 1. The probability of progression free survival of the patients at 10 years



Number at risk

Age<50y	13	10	9	7	5	5	2
Age 50-60y	9	7	5	1	1	0	0
Age>60 y	9	7	5	3	2	1	0
	0	20	40	60	80	100	120

Figure 2. The probability of progression free survival of the patients with age <50 y, 50-60 y and >60 y (p=0.096)



Number at risk

Age ≤60y	22	17	14	8	6	5	2
Age>60 y	9	7	5	3	2	1	0
	0	20	40	60	80	100	120

Figure 3. The probability of progression free survival of the patients with age ≤60y and age >60 y (p=0.034)

DISCUSSION

Despite the enormous developments in targeted and immunotherapies in malignant disorders, PNAs has remained the mainstay of HCL treatment for a long while.[6-13] In this cohort as well, the majority of the patients (88%) were applied cladribine in the first line and additonally rituximab was added to the regimen in two of these patients. The response rate was over 90% in patients who took only cladribin that is in consistent with the previous literature.[6-13] However, the progression was observed in 25.8% of the patients, 7 of whom treated solely by cladribine. Moreover, PFS at 10 years was 33% which could not be ignored. The response rates to cladribin are fairly well which retains its priority in HCL treatment. However progression is the major concern in HCL patients treated by just cladribine.[6-8,10-13] Else et al.[6] focused on the favorable effects of obtaining CR on the relapse free survival. Also Broccoli, et al.[9] and Else et al.[13] showed that time to next treatment was better in patients achieving CR compared to patients with PR. Furthermore, achievement of MRD negativity after first line treatment was found to be related to longer relapse free and treatment free survival in HCL patients.[4,5,14] Hereby, first line treatment should be started with the intention of attainment deepest response. In recent years, addition of rituximab to PNA in the first line has provided the desired improvement in sustained responses in HCL.[2-5] The activity of rituximab was first tested as monotherapy in relapse setting however resulting in a modest efficacy.[15-17] Subsequently, rituximab was combined with PND in the treatment of relapsed HCL patients and demostrated to be more effective.[18,19] Eventually, rituximab-cladribine combination was given in the first line treatment of HCL providing more prononcued disease free survival which was an issue to be solved in HCL patients.[20-23] At this

point rituximab can be used concurrently or delayed after cladribine. Chihara et al.[22] demonstrated that concurrent use of rituximab with cladribine provided durable response compared to the delayed use of rituximab after cladribine. In our clinics, we started to apply rituximab and cladribine in the first line recently because of the health insurance payment terms.

In this cohort a notworthy point is the age distrubution of the patients that is, a significant portion of the patients (42.4%) were under 50 years and 30.3% were over 60 years. We also exhibited different PFS according to the age groups which was inferior in young and especially in older patients. Rosenberg et al.[12] investigated the outcomes of cladribine treatment in young HCL patients and found high rates of CR with durable responses. Hermel et al.[24] studied on elderly HCL patients and showed similar results of high CR rates with durable responses. However both studies did not have any other group as control opposite the age group they chose. It would make more sense to compare the treatment outcomes of young, old and middle age groups.

Limitations

This study was retrospective with a relatively low number of patients which caused a remarkable limitation. Also, lack of adequate data about the bone marrow biopsies after treatment, encumbered to evaluate the CR rates.

CONCLUSION

As a resut, cladribine was verified to be an effective treatment modality in HCL with high response rates. But, PFS was quite low at long term. With the introduction of rituximab-cladribine combination in the first line treatment of HCL, the real world data is required particularly for long term results. Another important point is the differences regarding PFS between age groups, exclusively poor results in older patients. From this point of view, when investigating the efficacy of a treatment modality in HCL, it would be more appropriate to evaluate the durability of response according to the age groups. Thus, administration of a treatment without a durable response would be prevented in elderly patients who are more fragile and prone to the toxicity of drugs.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Scientific Researches Ethics Committee of Adana City Training and Research Hospital (Date: 15.01.2026, Decision No: 983).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: ES; Design: ES; Control: ES, DD; Resources: NB; Materials: NB; Data Collection and/or Processing: ES, DD, BA, DYA, ZTK, ÇÜ, NB; Analysis and/or Interpretation: ES; Literature Review: ES, DD, BA, DYA, ZTK, ÇÜ, NB; Writing the Article: ES, DD; Critical Review: ES, DD, BA, DYA, ZTK, ÇÜ, NB.

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Original Article

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CMV reactivation after autologous stem cell transplantation: exploratory associations with transfusion burden and pre-transplant IMiD exposure[a]

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ABSTRACT

Aims: To evaluate the incidence and clinical impact of cytomegalovirus (CMV) reactivation and disease after autologous stem cell transplantation (ASCT), explore associations between transfusion burden, pre-transplant immunomodulatory drug (IMiD) exposure, and CMV reactivation, and identify subgroups that may warrant intensified surveillance.

Methods: Retrospective analysis of 188 CMV-seropositive ASCT recipients at Erciyes University between 2007–2016. CMV PCR was performed twice weekly for the first 100 days. Reactivation was defined as new PCR positivity after ASCT in a patient with a negative or undetectable pre-transplant PCR. Erythrocyte suspension (ES) and platelet suspension (PS) were analysed separately alongside combined transfusion burden, with patients receiving no blood products retained as the 0-unit reference group. Fisher exact and Chi-square tests were used (SPSS v16.0).

Results: CMV reactivation occurred in 44 patients (23.4%); 40 (90.9%) had asymptomatic DNAemia and 4 (9.1%) developed CMV disease. All reactivation events occurred within day +46. Refractory/progressive disease was associated with higher reactivation rates (50.0% vs 21.9%; p=0.056). Including the 0-unit reference group (n=186), ES ≥6 units was significantly associated with CMV reactivation (62.5% vs 21.9%; odds ratio [OR] 5.94, 95% confidence interval [CI]: 1.36–25.96; p=0.019), while PS (≥6 vs <6 units) alone was not (31.6% vs 22.8%; p=0.399). In an analysis restricted to pre-transplant IMiD exposure within the MM subgroup — the only analysis used to infer a protective association — reactivation occurred in 10.5% of exposed patients (n=19) versus 27.4% of IMiD-naive MM patients (n=84; OR 0.31, 95% CI 0.07–1.46; p=0.149), a non-significant trend. Because all CMV reactivation events occurred by day +46, before post-transplant IMiD maintenance is typically initiated (day +60–100), post-transplant IMiD exposure could not plausibly have influenced these events and was not used as a predictor of reactivation. Conditioning regimen was not associated with CMV reactivation across four regimen groups (BEAM, melphalan 200, melphalan 140, and other regimens) (p=0.863).

Conclusion: Refractory disease and high erythrocyte transfusion burden are strongly associated with CMV reactivation after ASCT, although the erythrocyte-transfusion association may partly reflect delayed immune recovery rather than a direct causal effect. ES was the transfusion parameter most consistently associated with reactivation; PS alone was not independently associated. Pre-transplant IMiD exposure showed a non-significant protective trend in the MM subgroup that requires confirmation in larger, prospective studies; the proposed NK-cell-mediated mechanism remains hypothetical pending direct immune-function data. Risk-stratified CMV monitoring may be warranted for high-risk subgroups, pending validation in contemporary, prospective cohorts.

Keywords: Autologous stem cell transplantation, cytomegalovirus, immunomodulatory drugs, erythrocyte transfusion, risk factors

[a]Parts of this study were presented as an oral presentation at the 10th Hematological Oncology Congress, 28–30 September 2023, Turkish Republic of Northern Cyprus.

INTRODUCTION

Cytomegalovirus (CMV) remains the most clinically significant viral pathogen following haematopoietic cell transplantation.[1] CMV seroprevalence exceeds 90% in Turkiye,[2] substantially higher than the ~50–60% reported in Western populations,[3] and reactivation after autologous HSCT (ASCT) is reported in 4–33% of seropositive recipients.[4-7] Although most episodes are asymptomatic, progression to CMV disease carries high mortality, and late

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reactivation has been linked to inferior survival.[8] Despite the well-established risk profile in allogeneic HSCT, risk factors for CMV reactivation in ASCT remain poorly defined,[9,10] and the clinical significance of asymptomatic DNAemia versus overt CMV disease in this setting is not fully resolved.

Immunomodulatory drugs (IMIDs)—thalidomide, lenalidomide, and pomalidomide—enhance NK-cell and T-cell activity through cereblon-mediated mechanisms[11,12] and may confer antiviral protection; however, whether this effect depends on the timing of IMID exposure relative to transplantation has not been evaluated. Similarly, the relative contribution of erythrocyte versus platelet transfusion burden to CMV reactivation risk remains poorly characterised. This study evaluates these questions in a large single-centre ASCT cohort, with particular attention to the temporal plausibility of the IMiD association and to the extent to which transfusion-related associations may reflect residual confounding by disease and treatment intensity rather than a direct effect.

METHODS

Ethics

This study was approved by the Clinical Researches Ethics Committee of Erciyes University (Date: 15.09.2017, Decision No: 2017/430). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

All patients undergoing ASCT between January 2007 and December 2016 (n=352) were screened. Inclusion required CMV seropositivity and at least twice-weekly CMV PCR monitoring during the first 100 days post-ASCT. After day +100, PCR was repeated on clinical suspicion. A total of 188 patients were included.

CMV Monitoring and Definitions

CMV DNAemia was defined as PCR ≥100 IU/ml; CMV disease required clinical symptoms or tissue confirmation.[13] Preemptive therapy (intravenous ganciclovir or oral valganciclovir; foscarnet for refractory cases) was initiated for viral loads >2,000 IU/ml or rising titres. No CMV prophylaxis was administered during the study period. As part of pre-transplant donor/recipient screening, baseline CMV serostatus and PCR were assessed; only patients with a negative or undetectable pre-transplant PCR were classified as having post-transplant CMV reactivation. The single patient with a positive PCR on day 0 had a documented negative pre-transplant PCR, confirming true post-transplant reactivation rather than pre-existing DNAemia.

Transfusion and IMID Analysis

All blood products were leukoreduced and irradiated. ES and PS volumes were recorded separately. Patients who received no blood products (n=28) were retained as the 0-unit reference category in transfusion analyses rather than excluded; two additional patients with recorded platelet but no recorded erythrocyte-transfusion data were excluded from ES-specific analyses only, giving an ES-evaluable n=186. IMID exposure (thalidomide, lenalidomide, or pomalidomide) and its timing relative to transplantation were recorded for MM patients. Because all CMV reactivation events occurred by day +46, well before post-transplant IMiD maintenance is typically initiated (day +60–100), the primary IMiD risk-factor analysis was restricted to pre-transplant IMiD exposure within the MM subgroup; post-transplant IMiD exposure was analysed descriptively only and was not used as a predictor of reactivation. One patient's diagnosis had been miscoded in the study database as non-Hodgkin lymphoma; chart review confirmed a diagnosis of multiple myeloma, and the record was corrected prior to analysis (all analyses below therefore use the full, corrected cohort of n=188).

Statistical Analysis

Analyses were performed using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). Fisher exact and Chi-square tests were applied; $p<0.05$ was significant. Exact 95% CIs (Clopper-Pearson method) and bootstrap analysis (10,000 iterations) were performed for small subgroups.

RESULTS

Patient Characteristics and CMV Outcomes

Of 188 CMV-seropositive patients (mean age 52.8±13.2 years; 117 male [62.2%]), the most common diagnosis was MM (n=127, 67.6%), followed by NHL (n=27, 14.4%) and HL (n=15, 8.0%) (one patient's diagnosis, originally miscoded as NHL, was corrected to MM after chart review; see Methods). At ASCT, 138 (73.4%) were in CR, 40 (21.3%) in PR, 8 (4.3%) had refractory/relapsed disease, and 2 (1.1%) progressive disease. CMV reactivation occurred in 44 patients (23.4%): 40 (90.9%) had asymptomatic DNAemia and 4 (9.1%) developed CMV disease (2 gastrointestinal, 1 pulmonary, 1 febrile with biopsy-proven tissue invasion). The median day of first positive PCR was day +29 (range 0–46); all events occurred within day +46. Patient characteristics are summarised in Table 1.

Table 1. Patient demographics and clinical characteristics (n=188)

Characteristic	n	%
Gender, male	117	62.2
Age, mean±SD (years)	52.8±13.2	—
Diagnosis		
Multiple myeloma	127	67.6
Non-Hodgkin lymphoma	27	14.4
Hodgkin lymphoma	15	8.0
Other diagnoses	19	10.1
Disease status at ASCT		
Complete remission (CR)	138	73.4
Partial remission (PR)	40	21.3
Refractory/relapsed	8	4.3
Progressive disease	2	1.1
CMV IgG seropositive	188	100.0
IMID-exposed (MM subgroup)	43/127	33.9

ASCT: Autologous stem cell transplantation, CMV: Cytomegalovirus, IMID: Immunomodulatory drug, MM: Multiple myeloma, SD: Standard deviation.

Risk Factors for CMV Reactivation

Disease status at ASCT showed a clinically meaningful association with CMV reactivation: rates were 22.5% (CR), 20.0% (PR), 62.5% (refractory/relapsed), and 0% (progressive). Comparing remission (CR+PR, n=178) with refractory/progressive disease (n=10): 21.9% vs 50.0% (p=0.056). This difference did not reach conventional statistical significance,

reflecting the small size of the refractory subgroup. Conditioning regimen was not independently associated with CMV reactivation (BEAM 27.5% [n=51], melphalan 200 21.9% [n=105], melphalan 140 20.0% [n=20], other regimens 25.0% [n=12]; four-group Chi-square p=0.863). Risk factor data are presented in Table 2.

Table 2. Disease status at ASCT and CMV reactivation rates

Disease status	Total (n)	CMV+(n)	Rate (%)	p
Complete remission (CR)	138	31	22.5	
Partial remission (PR)	40	8	20.0	
Refractory/relapsed	8	5	62.5	
Progressive disease	2	0	0.0	
Remission (CR+PR) vs refractory/progressive	178 vs 10	39 vs 5	21.9 vs 50.0	0.056*

*Fisher's exact test. CMV: Cytomegalovirus, CR: Complete remission, PR: Partial remission.

IMID Exposure and CMV Reactivation

After correcting one patient's diagnosis—miscoded in the study database as non-Hodgkin lymphoma but confirmed as multiple myeloma on chart review (n=188 throughout)—IMiD exposure was associated with a lower reactivation rate in the overall cohort (9.3% vs 27.6%; p=0.013) and the MM subgroup (9.3% vs 27.4%; p=0.022). IMID-exposed and IMID-naive MM patients had similar mean ES transfusion volumes (0.8 units each), arguing against ES burden as a confounding variable. Because all CMV reactivation events occurred by day +46—before post-transplant IMiD maintenance is typically initiated (day +60–100)—post-transplant IMiD exposure cannot plausibly have influenced these events and was not used as a predictor of reactivation. The primary risk-factor analysis was therefore restricted to pre-transplant IMiD exposure within the MM subgroup (n=19): reactivation occurred in 10.5% of pre-transplant IMiD recipients versus 27.4% of IMiD-naive MM patients (OR 0.31, 95% CI 0.07–1.46; p=0.149), a non-significant protective trend most likely reflecting limited statistical power. Post-transplant IMiD exposure (n=21; reactivation 9.5%) is presented in Table 3 for descriptive completeness only and was not used to infer a protective effect, given the temporal implausibility described above. IMiD timing could not be classified for 3 of the 43 MM IMiD-exposed patients because of incomplete treatment-date records. IMID data are summarised in Table 3.

Table 3. IMID exposure, timing, and CMV reactivation

Group	Total (n)	CMV+(n)	Rate (%)	p
All patients–IMID naive	145	40	27.6	0.013*
All patients–IMID exposed	43	4	9.3	
MM–IMID naive	84	23	27.4	0.022*
MM–IMID exposed	43	4	9.3	
IMID timing (MM exposed only)				
Pre-transplant IMID	19	2	10.5	1.000*
Post-transplant IMID	21	2	9.5	
IMID naive (MM reference)	84	23	27.4	—

*Fisher's exact test. CMV: Cytomegalovirus, IMID: Immunomodulatory drug, MM: Multiple myeloma.

Transfusion Burden and CMV Reactivation

Retaining the 28 patients who received no blood products as the 0-unit reference group (evaluable n=186), total transfusion volume was significantly associated with CMV reactivation (17.6% [0 units], 22.3% [1–5 units], 29.4% [6–10 units], 53.8% [≥11 units]; four-group p=0.048). ES ≥6 units remained strongly associated with reactivation: 62.5% (95% CI: 24.5–91.5%) vs 21.9% (95% CI: 16.1–28.7%) for ES <6 units, including the 0-unit patients (OR 5.94, 95% CI: 1.36–25.96; p=0.019). Bootstrap analysis (10,000 iterations) confirmed a similar median risk difference of 41.2% (95% CI: 4.8–70.6%). Using the same ≥6 vs <6-unit threshold, PS was not independently associated with CMV reactivation (31.6% vs 22.8%; OR 1.57; p=0.399). Two patients who received platelet but no recorded erythrocyte transfusion were excluded from ES-specific analyses because unit counts were unavailable. Transfusion data are presented in Table 4.

Table 4. Transfusion burden and CMV reactivation (n=160 patients receiving replacement therapy)

Group	n	CMV+(n)	Rate (%)	p
Total blood products				**0.043†**
≤5 units	130	29	22.3	
6–10 units	17	5	29.4	
≥11 units	13	7	53.8	
Erythrocyte suspension (ES)				**0.028***
ES <6 units	150	36	24.0 (95% CI: 17.4–31.6)	
ES ≥6 units	8	5	62.5 (95% CI: 24.5–91.5)	
Platelet suspension (PS)—any volume	160	41	25.6	0.429 NS†

*Fisher's exact test, † Chi-square test. CI: Confidence interval, CMV: Cytomegalovirus, ES: Erythrocyte suspension, NS: Not significant, PS: Platelet suspension.

DISCUSSION

This retrospective analysis of 188 CMV-seropositive ASCT recipients demonstrates a reactivation rate of 23.4%, consistent with contemporary cohorts.[8,14] All events occurred within day +46, confirming the adequacy of the 100-day monitoring window. The large majority of reactivation events (40/44, 90.9%) represented asymptomatic DNAemia rather than CMV disease (4/44, 9.1%), raising the question of whether DNAemia alone constitutes a clinically meaningful endpoint or primarily a virological marker. Because our retrospective dataset did not capture survival, transplant-related mortality, or length of hospital stay, we could not directly test the prognostic impact of reactivation in this cohort. Lee et al.[8] reported that CMV reactivation after ASCT was independently associated with inferior overall survival in a comparable population; our findings should be interpreted in that context — while the reactivation rate we observed is consistent with contemporary series, whether it independently affects outcomes in our own cohort remains unresolved and is an important direction for prospective follow-up incorporating survival endpoints.

Refractory/progressive disease at ASCT was associated with a clinically meaningful but statistically non-significant increase in CMV reactivation (50.0% vs 21.9%; p=0.056), likely reflecting limited power due to the small subgroup size (n=10). Conditioning regimen (BEAM, melphalan 200, melphalan 140, and other regimens) was not an independent predictor (p=0.863), though the strong collinearity between

diagnosis and regimen (MM→melphalan; lymphoma→BEAM) limits independent assessment of conditioning effects.

ES transfusion burden, analysed with the 0-unit reference group retained, was significantly associated with CMV reactivation (OR 5.94, 95% CI 1.36–25.96; p=0.019), while PS, evaluated using the same ≥6-unit threshold, was not independently associated (p=0.399). This association should not be interpreted as evidence of a direct causal effect: patients requiring higher ES volumes are also more likely to have undergone more intensive chemotherapy, experienced more severe mucositis, remained neutropenic longer, or engrafted later—factors not captured in this retrospective dataset (engraftment timing, CD34+ cell dose, mucositis grade, and duration of febrile neutropenia were unavailable). ES burden is therefore best regarded as a strongly associated marker of delayed immune recovery and greater treatment intensity rather than an independently confirmed causal risk factor. Even with standard leukoreduction, erythrocyte preparations may also exert direct immunosuppressive effects through soluble mediators and NK/T-cell suppression,[15] though this mechanism remains speculative in the absence of immune-function data in our cohort. Similar associations between immune dysregulation and CMV reactivation have also been described outside the transplant setting, in critically ill patients.[16]

The post-transplant IMiD subgroup should not be interpreted as evidence of a 'timing-independent' protective effect, because post-transplant IMiD maintenance (typically initiated day +60–100) could not plausibly have influenced CMV reactivation events that had already occurred by day +46. Restricting the analysis to pre-transplant IMiD exposure in the MM subgroup (n=19), we observed a non-significant protective trend (10.5% vs 27.4% in IMiD-naive MM patients; p=0.149) that did not reach statistical significance, most likely because of limited sample size; this finding is hypothesis-generating rather than confirmatory. A biologically plausible mechanism has been proposed in vitro: lenalidomide lowers the activation threshold of NK cells through cortical actin remodelling,[17] which could in principle produce a durable antiviral immune state. However, our dataset lacked NK-cell counts, NK-cell functional assays, T-cell subset data, and broader immune reconstitution measures, so this mechanism remains speculative and unconfirmed in our cohort and should be regarded as a hypothesis for future mechanistic studies rather than an established explanation.

An additional consideration is the applicability of these findings to current clinical practice. Patients in this cohort underwent ASCT between 2007 and 2016, a period that predates several major changes in CMV management, including risk-based individualised monitoring strategies,[18-22] more sensitive quantitative PCR assays, letermovir prophylaxis (not used in our cohort),[23,24] and newer therapeutic options such as maribavir for refractory or resistant CMV.[25,26] Contemporary practice increasingly relies on serostatus- and risk-based stratification[27] and risk-adapted surveillance; comparable strategies are less well defined specifically for ASCT recipients, for whom our data suggest a subset—patients with refractory/progressive disease or high ES requirements — could plausibly benefit from closer monitoring. Because CMV PCR thresholds, preemptive-therapy triggers, and supportive care have evolved since 2016, the absolute reactivation rates reported here should be interpreted as reflecting practice patterns of that era, and prospective validation in a contemporary cohort using current monitoring protocols and updated guidance[22] is warranted before these findings inform current surveillance policy.

Limitations

The retrospective single-centre design and small critical subgroups (refractory/progressive disease n=10; ES ≥6 units n=8; pre-transplant IMiD-exposed n=19) precluded multivariable adjustment, and all reported associations are unadjusted and should be interpreted as exploratory. We were unable to evaluate several parameters that plausibly influence both transfusion requirements and CMV reactivation risk, including neutrophil and platelet engraftment day, CD34+ cell dose, mucositis grade, and duration of febrile neutropenia; consequently, the association between ES burden and CMV reactivation may partly reflect delayed immune recovery rather than a direct transfusion-related effect. Data on corticosteroid and other immunosuppressive therapies were available for all patients; however, calculation of precise cumulative doses was not feasible from retrospective records. Importantly, all patients received similar standard-of-care steroid regimens as part of conditioning and supportive care, suggesting broadly comparable steroid exposure levels across groups, which limits the likelihood of major steroid-related confounding. Transfusion volume was analysed as a cumulative summary measure; time-varying modelling was beyond the scope of this study. Survival, transplant-related mortality, and length of hospital stay were not systematically captured in this retrospective database, precluding outcome analyses; this is an important limitation given uncertainty about the clinical significance of asymptomatic CMV DNAemia and should be addressed in future prospective studies with survival follow-up. All CMV reactivation events occurred within day +46 and no late reactivation was detected, supporting the adequacy of the 100-day monitoring window; the primary IMiD analysis (pre-transplant exposure, MM subgroup, n=19) showed a non-significant protective trend (10.5% vs 27.4%, p=0.149), reflecting reduced statistical power. The proposed NK-cell-mediated mechanism underlying the IMiD association is not supported by direct immune-function data (NK-cell counts, NK-cell functional assays, T-cell subsets, or immune reconstitution measures) in this cohort and remains hypothetical. This cohort was treated between 2007 and 2016, and CMV monitoring and treatment practices have since evolved; the generalisability of absolute reactivation rates to contemporary practice is discussed above. Despite these limitations, the systematic twice-weekly monitoring protocol and uniform transfusion policy provide a dataset for exploratory risk factor identification in this understudied population.

CONCLUSION

Refractory disease and high erythrocyte transfusion burden are strongly associated with CMV reactivation after ASCT, although the erythrocyte-transfusion association may partly reflect delayed immune recovery rather than a direct causal effect. ES was the transfusion parameter most consistently associated with reactivation; PS alone is not independently associated. Pre-transplant IMiD exposure showed a non-

significant protective trend in the MM subgroup that requires confirmation in larger, prospective studies; the proposed NK-cell-mediated mechanism remains hypothetical pending direct immune-function data. Risk-stratified CMV surveillance may be warranted, with intensified monitoring for patients with refractory disease or high ES requirements; these exploratory findings should be validated in contemporary, prospective cohorts before informing clinical monitoring policy.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of Erciyes University (Date: 15.09.2017, Decision No: 2017/430).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: MI, LK; Design: MI, LK, SG; Control: MI, LK, SG, MÇ; Resources: MI, LK; Materials: MI, LK, SG; Data Collection and/or Processing: MI, LK, SG, MÇ; Analysis and/or Interpretation: MI, LK; Literature Review: MI, LK, SG; Writing the Article: MI, LK; Critical Review: MI, LK, SG, MÇ.

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The relationship between serum vitamin B12 level and fibroadenoma in adolescent female patients: a retrospective case-control study[a]

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ABSTRACT

Aims: This study aimed to investigate serum vitamin B12 levels in adolescent female patients diagnosed with fibroadenoma and to evaluate whether a significant difference exists between fibroadenoma patients and healthy controls.

Methods: This retrospective case-control study was conducted between 2018 and 2023. A total of 46 adolescent female patients diagnosed with fibroadenoma based on ultrasonographic (USG) evaluation in accordance with ACR guidelines, with histopathological confirmation in eight cases (17%), and 46 age- and gender-matched controls were included. Hematological parameters were analyzed alongside serum vitamin B12 levels. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of fibroadenoma. A decision tree model was additionally constructed to define clinically meaningful threshold values.

Results: The mean serum vitamin B12 level was significantly lower in the fibroadenoma group compared to controls (304.54±79 pg/ml vs. 407±137 pg/ml; p<0.001). Among fibroadenoma patients, 88.9% had vitamin B12 levels below 300 pg/ml. The proportion of patients with vitamin B12 levels exceeding 340 pg/ml was 18.9% in the fibroadenoma group versus 81.1% in controls, a statistically significant difference (p=0.019). Multivariate logistic regression identified low serum vitamin B12 level as an independent predictor of fibroadenoma. Decision tree analysis confirmed vitamin B12 as the primary discriminating variable, with red cell distribution width (RDW) emerging as a secondary node.

Conclusion: To our knowledge, this is the first study to investigate serum vitamin B12 levels in adolescent patients with fibroadenoma. The significantly lower vitamin B12 levels observed in fibroadenoma patients compared to controls suggest a potential role of vitamin B12 in the pathogenesis of this benign breast lesion. The identified 300 pg/ml threshold suggests that serum vitamin B12 may serve as a simple and accessible biomarker for fibroadenoma risk stratification in adolescents. Prospective multicenter studies incorporating functional B12 markers such as homocysteine and methylmalonic acid are needed to validate these findings

Keywords: Fibroadenoma, vitamin B12, adolescent, benign breast disease

[a]This study was presented as an oral presentation at the 45th Pediatrics Days, 24th Pediatric Nursing Days, and 1st Pediatric Dietetics Days, İstanbul, April 25–28, 2023.

INTRODUCTION

Fibroadenoma is the most common benign breast neoplasm in adolescents and young adult females. These lesions account for approximately 68% of all breast masses and 44–94% of biopsy-evaluated breast lesions in this age group.[1] The etiology of this lesion, characterized by simultaneous proliferation of stromal and epithelial components, is thought to involve increased estrogen sensitivity, local growth factors, and hormonal variables. Although fibroadenomas are classified as benign lesions, the potential for malignant transformation in cases containing proliferative epithelial changes should not be overlooked. Dupont et al.[2] reported that the risk of invasive breast cancer was 2.17-fold higher in females with fibroadenoma compared to controls, rising to 3.10 in complex fibroadenoma. In the systematic review by El-Wakeel and Umpleby,[3] fibroadenoma with atypical changes was reported to carry a 0.12–0.3% risk of malignant transformation.

Vitamin B12 is an essential vitamin that plays a critical role in one-carbon metabolism, DNA synthesis, and methylation pathways.[4] As a cofactor of methionine synthase,

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it supports the biosynthesis of S-adenosylmethionine (SAM), the principal methyl group donor for DNA, RNA, and histone methylation. It has been proposed that B12 deficiency may predispose rapidly dividing tissues such as the breast to proliferative changes through homocysteine accumulation, DNA strand breaks, aberrant methylation of tumor suppressor genes, and genomic instability.[4,5] During adolescence, the rapid rise in estrogen levels increases the proliferative capacity of the breast gland; vitamin B12 deficiency at this stage may, through its role as a critical cofactor in DNA methylation and synthesis, create the epigenetic milieu that supports cellular proliferation.

Existing studies have examined the relationship between vitamin B12 and breast gland pathology predominantly in the context of invasive breast cancer.[6-10] Although inconsistent findings have been reported in prospective studies and meta-analyses, the relationship between serum B12 levels and the presence of benign breast lesions such as fibroadenoma has not yet been investigated. To our knowledge, no study has directly examined the association between serum vitamin B12 level and fibroadenoma. This gap in the literature is clinically significant, particularly given the adolescent population. Considering that vitamin B12 deficiency is highly prevalent in adolescents and that the breast gland in this age group is especially sensitive to hormonal stimuli, investigation of this relationship carries considerable clinical and biological importance.

In this context, exploring the potential role of vitamin B12 in fibroadenoma pathogenesis during adolescence is of value both for elucidating biological mechanisms and for identifying clinical risk markers. Accordingly, this study aimed to investigate the association between serum vitamin B12 levels and fibroadenoma in adolescent female patients, and to evaluate the independent predictive role of serum vitamin B12 in fibroadenoma risk through logistic regression and decision tree analyses.

METHODS

This study was approved by the Scientific Researches Evaluation and Ethics Committee of Ankara Etlik City Hospital (Date: 27.11.2024, Decision No: AEŞH-BADEK-2024-1132). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective case-control study was conducted at a tertiary referral center. The fibroadenoma group was drawn from the department of pediatric surgery, and the control group was selected from the pediatric oncology outpatient clinic.

Medical records of adolescent female patients aged 10–19 years who presented to our clinic between 2018 and 2023 and were diagnosed with fibroadenoma based on ultrasonographic (USG) evaluation of a palpable breast mass were retrospectively reviewed. According to American College of Radiology (ACR) guidelines, USG is recommended as the primary imaging modality for the evaluation of palpable breast masses in females under 30 years of age, owing to its low radiation risk and high diagnostic accuracy.[11] Accordingly, diagnoses in our study were based on USG evaluation performed by experienced radiologists in accordance with the BI-RADS classification system. Cases with non-fibroadenoma diagnoses such as cyst, lipoma, or axillary lymphadenopathy were excluded. In eight patients (17%), additional histopathological confirmation was obtained, and pathology results were fully concordant with the USG diagnosis.

A total of 92 patients were included: 46 patients diagnosed with fibroadenoma (fibroadenoma group) and 46 age-matched controls with no breast pathology (control group). The control group comprised adolescent girls who presented to the outpatient clinic with lymphadenopathy during the same period, had no detectable breast pathology, and were not receiving vitamin B12 supplementation.

This approach was adopted to ensure retrospective access to documented serum vitamin B12 measurements, as vitamin B12 is systematically included in the standard haematological and biochemical panel for patients presenting to the Pediatric Oncology outpatient clinic at our institution. The following methodological advantages support the validity of this control group: (i) both groups were followed at the same tertiary referral center during the same study period under comparable socioeconomic conditions, minimising institutional confounding; (ii) the control group was rigorously selected by applying the same exclusion criteria used for the patient group, including known haematological disease, chronic inflammatory conditions, metabolic disorders, malignancy, and vitamin B12 supplementation; and (iii) the mean serum B12 level in the control group (408±138 pg/ml) was within the normal reference range, confirming that these individuals were metabolically representative of a healthy adolescent population.

The following exclusion criteria were applied: (i) history of haematological disease; (ii) chronic inflammatory disease; (iii) metabolic disorder (including thyroid dysfunction and diabetes mellitus); (iv) known malignancy; (v) regular vitamin B12 supplementation at the time of blood sampling; (vi) incomplete laboratory records at the time of diagnosis.

Serum vitamin B12 (pg/ml), haemoglobin (Hb, g/dl), mean corpuscular volume (MCV, fL), and red cell distribution width (RDW) values at the time of diagnosis were retrieved from the hospital information management system. All blood samples were collected by standard venous access and analysed at the same institution's biochemistry laboratory. Age at the time of laboratory testing was also recorded.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. As variables did not follow a normal distribution, non-parametric tests were used for group comparisons. Comparisons between the fibroadenoma and control groups were performed using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Data are presented as mean±standard deviation (SD) and median (interquartile range, IQR).

Univariate and multivariate logistic regression analyses were performed to identify independent predictors of fibroadenoma. To eliminate scale effects arising from different units of measurement and to improve comparability of effect sizes, z-score standardisation was applied to all continuous variables prior to logistic regression. Results are reported as odds ratios (OR) with 95% confidence intervals (95% CI).

A decision tree analysis (CHAID method) was performed to identify clinically meaningful threshold values for serum vitamin B12 levels. This method identifies statistically significant split points based on the Chi-square statistic without requiring parametric distributional assumptions. A p value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 92 adolescent female patients were included, comprising 46 with fibroadenoma and 46 age-matched controls. Demographic characteristics and laboratory values for both groups are presented in Table 1.

Table 1. Comparison of demographic and laboratory variables between the fibroadenoma and control groups (Mann-Whitney U test).

Variable	Control group (n=46)	Fibroadenoma group (n=46)	p value
Age at examination (years)			0.700
Mean±SD	14.15±3.29	14.78±1.86	
Median (IQR)	15.23 (11.01–16.81)	15.00 (13.67–16.00)	
Range	5.75–19.20	10.00–18.00	
Vitamin B12 (pg/ml)			<0.001
Mean±SD	408±138	305±79	
Median (IQR)	369 (324–430)	298 (254–326)	
Range	254–879	204–590	
Haemoglobin (g/dl)			0.400
Mean±SD	12.91±1.27	12.98±1.36	
Median (IQR)	13.20 (12.25–13.50)	13.40 (12.53–13.70)	
Range	9.00–15.10	9.20–14.80	
MCV (fL)			0.110
Mean±SD	82±6	83±7	
Median (IQR)	83 (79–86)	85 (81–88)	
Range	58–90	66–95	
RDW (%)			0.200
Mean±SD	14.06±1.70	13.86±1.77	
Median (IQR)	13.65 (13.00–14.58)	13.25 (12.73–14.48)	
Range	11.20–18.90	11.90–19.70	

n: Number, SD: Standard deviation, IQR: Interquartile range, MCV: Mean corpuscular volume, RDW: Red cell distribution width. p<0.05 was considered statistically significant.

No statistically significant difference was found between the groups with respect to age at examination. Mean age was 14.78±1.86 years in the fibroadenoma group (median: 15.00, IQR: 13.67–16.00, range: 10.00–18.00) and 14.15±3.29 years in the control group (median: 15.23, IQR: 11.01–16.81, range: 5.75–19.20) (p=0.700). This finding confirms successful age-matching between the two groups.

Serum vitamin B12 levels were significantly lower in the fibroadenoma group compared to controls (p<0.001). Mean vitamin B12 was 305±79 pg/ml (median: 298, IQR: 254–326) in the fibroadenoma group versus 408±138 pg/ml (median: 369, IQR: 324–430) in controls. The median difference of 71 pg/ml between groups is both clinically and statistically meaningful.

No statistically significant differences were found between the groups with respect to haemoglobin, MCV, or RDW (p=0.400, p=0.110, and p=0.200, respectively). All intergroup comparisons are summarised in Table 1.

In univariate logistic regression analysis after z-score standardisation, vitamin B12 demonstrated a statistically significant and strong inverse association with fibroadenoma (OR=0.22, 95% CI: 0.08–0.46, p<0.001). This finding indicates that each one SD increase in vitamin B12 level reduces the odds of fibroadenoma by approximately 78%.

In the multivariate logistic regression model including all variables, vitamin B12 remained a significant independent predictor of fibroadenoma (OR=0.17, 95% CI: 0.06–0.39, p<0.001). Age, haemoglobin, MCV, and RDW were not statistically significant in either model (all p>0.05). Results of both analyses are presented together in Table 2.

Table 2. Univariate and multivariate logistic regression analysis results for fibroadenoma (after z-score standardisation)

Variable	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age at examination	1.27	0.84–1.96	0.262	0.92	0.53–1.54	0.700
Vitamin B12	**0.22**	**0.08–0.46**	**<0.001**	**0.17**	**0.06–0.39**	**<0.001**
Haemoglobin	1.05	0.70–1.60	0.804	0.73	0.34–1.49	0.400
MCV	1.24	0.82–1.93	0.321	1.47	0.66–3.45	0.400
RDW	0.89	0.58–1.34	0.574	0.98	0.53–1.79	>0.900

OR: Odds ratio, CI: Confidence interval, MCV: Mean corpuscular volume, RDW: Red cell distribution width. Each OR reflects the effect of a one standard deviation increase in the corresponding variable on the probability of fibroadenoma. Bold: statistically significant variable.

Decision tree analysis (CHAID method) identified serum vitamin B12 as the primary and strongest discriminating variable based on Chi-square split points. This finding is concordant with the logistic regression results.

At the root node, the vitamin B12 threshold was determined to be 300 pg/ml. Of the 27 patients with vitamin B12 levels below 300 pg/ml, 24 (88.8%) had fibroadenoma. In the 28 patients with vitamin B12 between 300 and 340 pg/ml, this rate decreased to 53.6% (15 patients), while it fell to 18.9% in those with levels above 340 pg/ml (Figure). These findings indicate a clear dose-response relationship between serum vitamin B12 level and fibroadenoma risk.

At the second level of analysis, RDW emerged as a secondary determinant within the subgroup with vitamin B12 <340 pg/ml. Fibroadenoma was identified in 15 of 16 patients (93.75%) with vitamin B12 <340 pg/ml and RDW ≤13.8%. Subgroup results from the decision tree analysis are summarised in Table 3.

DISCUSSION

In this retrospective case-control study, serum vitamin B12 level was found to be independently and significantly

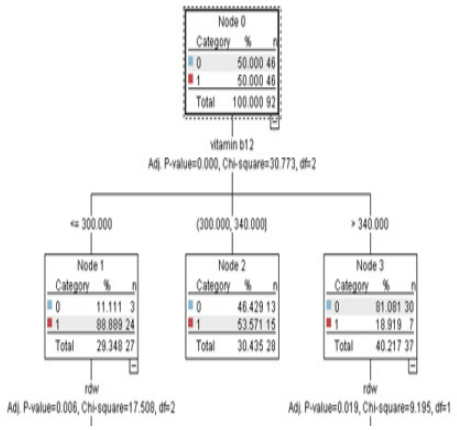


Figure. Decision tree model illustrating the discrimination of fibroadenoma and control groups by serum vitamin B12 levels. The root node is split at 300 pg/ml and 340 pg/ml as primary threshold points. 0: control group; 1: fibroadenoma group.

Table 3. Distribution of fibroadenoma by serum vitamin B12 threshold values according to decision tree analysis (CHAID method)

Vitamin B12 subgroup	No. of patients (n)	Fibroadenoma (n)	Fibroadenoma rate (%)
B12<300 pg/ml	27	24	88.8%
300≤B12 < 340 pg/ml	28	15	53.6%
B12≥340 pg/ml	37	7	18.9%
B12<340 pg/ml and RDW ≤ 13.8%*	16	15	93.75%

n: Number, RDW: Red cell distribution width. *Subgroup showing co-occurrence of B12 <340 pg/ml and RDW ≤13.8%

associated with the presence of fibroadenoma in adolescent female patients. Mean serum vitamin B12 was markedly lower in the fibroadenoma group than in controls (305±79 pg/ml vs. 408±138 pg/ml; p<0.001), and this association persisted as an independent predictor in both univariate (OR=0.22, 95% CI: 0.08–0.46) and multivariate logistic regression analyses (OR=0.17, 95% CI: 0.06–0.39). Decision tree analysis further identified vitamin B12 as the primary discriminating variable, revealing that values below 300 pg/ml were associated with a marked increase in fibroadenoma risk. To our knowledge, this is the first study to evaluate serum vitamin B12 level specifically in the context of fibroadenoma in adolescent female patients, and this constitutes the primary novelty of our work.

Fibroadenoma is a benign breast tumour composed of stromal and epithelial components and represents the most common breast lesion in adolescents and young adult females.[1] Its etiology is thought to involve hormonal, nutritional, and metabolic variables. Although classified as a benign lesion, fibroadenoma has been shown to be associated with long-term breast cancer risk. Dupont et al.[2], in a retrospective cohort study of 1,835 fibroadenoma patients, reported a 2.17-fold increase in invasive breast cancer risk compared to controls, rising to 3.10 in complex fibroadenoma and to 3.88 in the presence of proliferative disease in adjacent parenchyma. El-Wakeel and Umpleby's[3] systematic review emphasized that fibroadenoma with atypical changes carries a 0.12–0.3% potential for malignant transformation, with this risk persisting for more than 20 years after diagnosis. These findings underscore the clinical importance of investigating underlying metabolic variables in fibroadenoma and support the biological rationale of our study.

The majority of existing studies have examined the relationship between vitamin B12 and invasive breast cancer rather than benign breast disease, with inconsistent results. Wu et al.[6], in a prospective nested case-control study using the Washington County serum bank, reported an approximately fourfold increase in breast cancer risk among postmenopausal females in the lowest quintile of serum B12 (matched OR=4.00, 95% CI: 1.05–15.20). Lajous et al,[8] in a case-control study of 475 breast cancer patients and 1,391 controls, found that the odds of breast cancer were approximately 68% lower in the highest quintile of vitamin B12 intake compared to the lowest (OR=0.32, 95% CI: 0.22–0.49). In contrast, Houghton et al.[9] found no significant association between plasma B12 and breast cancer risk in their prospective analysis within the Nurses' Health Study. Zeng et al.[10] likewise found no significant effect of vitamin B12 intake on breast cancer risk in a meta-analysis of 27 studies (RR=0.99, 95% CI: 0.94–1.04). Essén et al.[12] also reported no significant association between serum B12 and breast cancer risk in the prospective Swedish AMORIS cohort. By contrast, Haghighat et al.[13] reported that serum B12 levels were significantly higher in breast and colon cancer patients than in controls and correlated positively with tumour stage; this may reflect a divergence in cobalamin metabolism in invasive malignancies, biologically distinct from the low B12 profile seen in benign lesions such as fibroadenoma.

The inconsistencies across studies may be attributable to differences in study design, population characteristics (age, menopausal status, ethnicity), the use of dietary intake rather than serum B12 as the primary metric, and, most importantly, the fundamental biological differences between fibroadenoma and invasive breast cancer. The present study contributes to filling this gap in the literature by being the first to examine this association specifically in an adolescent population with fibroadenoma.

When considering the plausible mechanisms underlying the association between vitamin B12 and fibroadenoma, the vitamin's role in one-carbon metabolism is particularly prominent. Vitamin B12, as a cofactor of methionine synthase, catalyses the conversion of homocysteine to methionine from 5-methyltetrahydrofolate; this reaction maintains the methionine pool necessary for the biosynthesis of SAM, the principal methyl group donor for DNA, RNA, and histone methylation. Lyon et al.[4] emphasised that vitamin B12 in its methylcobalamin form is a critical component of the methionine cycle, and that disruption of this pathway may adversely affect DNA methylation regulation. Plazar and Jurdana[5] proposed that B12 deficiency increases homocysteine accumulation, which may lead to DNA damage and hypermethylation of tumour suppressor genes. Choi7 suggested that B12 deficiency may impair thymidine and purine synthesis, causing imbalances in the deoxyribonucleotide pool and ultimately resulting in DNA strand breaks. Taken together, these mechanisms suggest that B12 deficiency may predispose rapidly dividing tissues such as the breast to genomic instability; however, further studies are needed to elucidate the specific role of these mechanisms in fibroadenoma pathogenesis.

The absence of significant differences in haemoglobin, MCV, and RDW between the two groups is a noteworthy finding.

This suggests that patients in the fibroadenoma group did not present with clinically overt B12 deficiency, yet relatively lower serum B12 levels may be associated with breast gland pathology. This finding implies that serum B12 may exert biological effects at the tissue level without necessarily falling to levels that produce haematological changes, highlighting the need to assess functional B12 deficiency beyond standard haematological parameters. Vashi et al,[14] in a study of 316 cancer patients, emphasised that serum B12 alone may be insufficient to reflect metabolic deficiency, and that functional markers such as methylmalonic acid and homocysteine provide more reliable assessment of true B12 status.

Limitations

Several methodological limitations of this study must be acknowledged when interpreting its findings. The relatively small sample size (n=46 per group) may have limited the statistical power of the logistic regression model and the generalisability of the decision tree analysis; validation in larger samples is warranted. The fact that fibroadenoma diagnoses were based predominantly (83%) on USG findings, with histopathological confirmation in only eight patients (17%), represents a methodological limitation, although ACR guidelines recognise USG as the primary and sufficient diagnostic method in the adolescent age group.[11] Due to the retrospective design, functional B12 markers such as methylmalonic acid, homocysteine, folate, and vitamin B6 could not be measured, and Vashi et al.[14] have highlighted that serum B12 alone may be insufficient to reflect functional deficiency. The inability to control for potential confounders such as body-mass index, dietary habits, socioeconomic status, and menstrual irregularity due to the retrospective design limits the interpretation of the observed association, as does the single-centre nature of the study. However, the fact that the control group comprised patients followed at the same institution under comparable conditions partially mitigates the risk of selection bias. Despite these limitations, our study makes an original contribution to the literature as the first study to systematically evaluate serum vitamin B12 levels in adolescent patients with fibroadenoma. The findings suggest that serum vitamin B12 may be a candidate as a simple, low-cost, and accessible biomarker for fibroadenoma risk assessment. The 300 pg/ml threshold identified by decision tree analysis may represent a clinically meaningful cut-off value; nonetheless, prospective validation in larger cohorts is required before any clinical recommendation can be made.

The selection of the control group from patients presenting with lymphadenopathy to the pediatric oncology outpatient clinic warrants consideration as a potential source of selection bias. When lymphadenopathy is associated with underlying inflammation or other systemic pathology, it may theoretically influence B12 metabolism. However, individuals with known haematological disease, chronic inflammatory conditions, or malignancy were excluded through the application of predefined exclusion criteria. Furthermore, the mean serum B12 level in the control group (408±138 pg/ml) fell within the normal reference range, supporting the premise that these individuals were metabolically representative of a healthy adolescent population. Nevertheless, future prospective studies employing more homogeneous control groups recruited from general outpatient settings will be important in addressing this limitation.

CONCLUSION

As a result, this study is the first, to our knowledge, to investigate the association between serum vitamin B12 levels and fibroadenoma in adolescent female patients. The significantly lower vitamin B12 levels and the 300 pg/ml threshold identified by decision tree analysis suggest that vitamin B12 may play a biologically meaningful role in fibroadenoma pathogenesis and may serve as a simple, accessible, and low-cost biomarker candidate for risk stratification in adolescents. Prospective, multicentre studies incorporating functional B12 markers such as homocysteine and methylmalonic acid are needed to validate these findings and establish evidence-based clinical recommendations.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Scientific Researches Evaluation and Ethics Committee of Ankara Etlik City Hospital (Date: 27.11.2024, Decision No: AEŞH-BADEK-2024-1132).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: GŞ; Design: MBH, GŞ; Control: GŞ, ŞY; Resources: ŞY, AF; Materials: MBH, CK; Data Collection and/or Processing: MBH; Analysis and/or Interpretation: MBH, GŞ; Literature Review: MBH; Writing the Article: MBH; Critical Review: MBH, ŞY, SE, CK, AF, GŞ.

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Serum albumin as an independent predictor of early mortality in metastatic gastric cancer

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ABSTRACT

Aims: This study aims to evaluate the prognostic value of baseline clinical and laboratory parameters in predicting six-month early mortality among patients with metastatic gastric cancer.

Methods: In this retrospective observational study, 91 patients diagnosed with metastatic (stage IV) gastric adenocarcinoma between January 2016 and January 2026 were evaluated. The primary endpoint was mortality within the first six months following diagnosis. Univariate and multivariable logistic regression analyses were utilized to identify early mortality predictors, while receiver operating characteristic (ROC) curve analysis evaluated the predictive performance of serum albumin.

Results: During the follow-up period, 29 patients (31.9%) died within the first six months. Patients experiencing early mortality presented with significantly lower baseline serum albumin levels (28.6±7.7 vs 36.7±5.6 g/L, $p<0.001$) and higher C-reactive protein (CRP) levels. Although the lack of response to first-line chemotherapy, serum albumin, and CRP were significant in the univariate analysis, multivariable logistic regression revealed that baseline serum albumin level ($p<0.001$, odds ratio (OR): 0.84) was the sole independent risk factor predicting six-month mortality. Furthermore, ROC analysis determined an optimal cut-off value of ≤35 g/L for albumin, which demonstrated an 80% sensitivity and a 53% specificity (area under the curve (AUC): 0.80).

Conclusion: Pre-treatment serum albumin level was independently associated with six-month mortality in patients with metastatic gastric cancer and may represent an accessible and potentially useful prognostic marker. Given the moderate specificity of the identified cut-off, serum albumin should be considered as a complementary risk-stratification parameter rather than a stand-alone predictor.

Keywords: Gastric neoplasms, prognosis, survival analysis, biomarkers, nutritional status

INTRODUCTION

Gastric cancer is one of the most common cancers. However, except in endemic regions, there are no routine screening programs; in countries where screening is conducted, the disease is detected at an earlier stage.[1] Because it is generally asymptomatic, it is often detected at a locally advanced or metastatic stage and has a poor prognosis.[2]

The prognosis is poor in advanced-stage gastric cancer. In fact, survival is quite short in some patient groups. Studies have identified various factors associated with short survival. Surgery is not beneficial in the metastatic stage, and factors influencing mortality are currently being investigated.[3] Although treatment regimens have improved, it remains a cancer type with a high mortality rate.[4]

Various factors have been examined to investigate the reasons for the poor prognosis in patients with stomach cancer. In these analyses, various scoring systems were developed based on patients' disease stage, laboratory parameters, and clinicopathological characteristics, and the impact of these scores on mortality was investigated.[5,6]

Among laboratory parameters, the effect of serum albumin level on survival has also been examined. Known to be a negative acute-phase reactant, serum albumin levels provide insight into the patient's nutritional status and physiological reserve; they have also been found to be closely associated with mortality in most gastrointestinal tract (GIT) cancers. In the meta-analysis conducted, albumin and globulin levels were examined, and a scoring system was applied. It was demonstrated that low albumin levels and high globulin levels have a negative impact on survival. The albumin-to-globulin ratio was analyzed, and it was found that the lower the albumin-to-globulin score, the worse the mortality outcome.[7]

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Early mortality remains a significant challenge in the treatment of metastatic gastric cancer, and identifying patients at high risk of early death may help guide treatment decisions and supportive care strategies. Although the prognostic value of serum albumin has been extensively reported in gastric cancer, most previous studies have focused on long-term overall survival across heterogeneous patient populations. Therefore, the present study aimed to evaluate the predictive role of baseline serum albumin and other clinical and laboratory parameters for short-term (six-month) mortality in patients with metastatic gastric cancer, including both de novo and recurrent metastatic disease.

METHODS

Ethics

This study was approved by the Non-interventional Clinical Researches Ethics Committee at the Van Yüzüncü Yıl University (Date: 17.04.2026, Decision No: 2026/04-04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Due to the retrospective nature of the study, the requirement for written informed consent was waived by the ethics committee. All patient data were anonymized and analyzed in accordance with data protection and confidentiality principles.

Study Design and Patient Population

This retrospective observational study was designed to evaluate the predictive value of baseline clinical and laboratory parameters for six-month mortality in patients with metastatic gastric cancer. Patients with metastatic gastric adenocarcinoma, including both de novo metastatic disease and recurrent metastatic disease, who were followed at the Medical Oncology Department of Van Yüzüncü Yıl University between January 2016 and January 2026 were evaluated.

Inclusion criteria were as follows: (1) age ≥18 years; (2) histopathologically confirmed gastric adenocarcinoma; (3) presence of metastatic disease, either de novo or recurrent; (4) receipt of first-line systemic treatment for metastatic disease; and (5) availability of sufficient clinical and laboratory data for the assessment of six-month mortality.

Exclusion criteria were as follows: (1) age <18 years; (2) histopathological diagnosis other than gastric adenocarcinoma; (3) absence of metastatic disease; (4) patients who did not receive first-line systemic treatment; and (5) incomplete clinical or follow-up data required for the study.

Data Collection

Clinical and demographic data were retrospectively obtained from the hospital electronic medical record system.

The collected variables included: Age, gender, presence of comorbid diseases, smoking status, weight loss, Eastern Cooperative Oncology Group (ECOG) performance status, tumor location, histopathological differentiation, Lauren classification, human epidermal growth factor receptor 2 (HER2) status, metastatic sites, first-line chemotherapy regimen, response to first-line therapy.

Baseline laboratory parameters recorded at the time of diagnosis included: Serum albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH), complete blood count parameters, tumor markers (CEA, CA19-9, and CA-125).

Treatment response was assessed radiologically according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Complete response (CR) and partial response (PR) were categorized as "response," whereas stable disease (SD) and progressive disease (PD) were categorized as "no response."

Study Endpoint

The primary endpoint of the study was mortality within the first six months after the diagnosis of metastatic disease. Accordingly, patients were divided into two groups:

- Patients who survived beyond 6 months after the diagnosis of metastatic disease
- Patients who died within 6 months after the diagnosis of metastatic disease

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics software (version 25.0, IBM Corp., Armonk, NY, USA).

Categorical variables were expressed as numbers and percentages and compared using the Chi-square test or Fisher's exact test. The distribution of continuous variables was assessed for normality using the Shapiro–Wilk test and visual inspection of distribution plots. Normally distributed continuous variables were presented as mean±standard deviation and compared using the independent-samples t-test.

To identify predictors of six-month mortality, logistic regression analysis was performed. Initially, all variables were evaluated using univariate logistic regression analysis. Variables with a p value<0.10 in the univariate analysis were included in the multivariable logistic regression model. Multivariable analysis was performed using the forward stepwise likelihood-ratio (LR) method.

To evaluate the predictive performance of serum albumin for early mortality, receiver operating characteristic (ROC) curve analysis was conducted. The optimal cut-off value was determined using the Youden index. p value<0.05 was considered statistically significant for all analyses.

RESULTS

A total of 91 patients with metastatic gastric cancer were included in the study. During the follow-up period, 29 patients (31.9%) died within the first 6 months, whereas 62 patients (68.1%) survived beyond 6 months.

Baseline Characteristics

The comparison of categorical variables according to six-month mortality is presented in **Table 1**. Patients who died within 6 months had a significantly worse ECOG performance status (p=0.048). In addition, the distribution of first-line chemotherapy regimens differed between the groups (p=0.042). In this retrospective cohort, FLOT was

Table 1. Comparison of categorical variables according to six-month mortality

Variable	Survived beyond 6 months (n=62)	Died within 6 months (n=29)	p
Gender			0.722
Female	17	9	
Male	45	20	
Comorbidity			0.114
Absent	18	4	
Present	44	25	
Smoking			0.580
No	24	13	
Yes	38	16	
Weight loss			0.104
No	30	9	
Yes	31	20	
ECOG performance status			0.048
0–1	33	9	
2–3	29	20	
Tumor location			0.482
Non-cardia	39	16	
Cardia	23	13	
Tumor differentiation			0.137
Well–moderate	36	12	
Poor	26	17	
Lauren classification			0.947
Intestinal	32	16	
Diffuse	18	8	
Mixed	12	5	
HER2 status			0.092
Negative	49	27	
Positive	13	2	
Disease presentation			0.734
De novo	49	22	
Recurrent	13	7	
Liver metastasis			0.909
Absent	35	16	
Present	27	13	
Lung metastasis			0.218
Absent	50	20	
Present	12	9	
First-line chemotherapy			0.042
mDCF	12	8	
FOLFOX	19	7	
FLOT	12	0	
Other	19	14	
Response to first-line therapy			0.003
No response	36	26	
Response	26	3	
Trastuzumab use			0.011
No	50	29	
Yes	12	0	

ECOG: Eastern Cooperative Oncology Group, HER2: Human epidermal growth factor receptor 2, mDCF: Modified docetaxel–cisplatin–5-fluorouracil, FOLFOX: 5-fluorouracil/leucovorin/oxaliplatin, FLOT: 5-fluorouracil/leucovorin/oxaliplatin/docetaxel. Data are presented as n. P values were calculated using the Chi-square test or Fisher's exact test.

administered to selected patients with de novo metastatic disease who were considered clinically fit for an intensive triplet chemotherapy regimen, at the discretion of the treating physician. The use of FLOT in these patients represented an individualized first-line treatment decision rather than a perioperative treatment strategy. Most importantly, lack of response to first-line chemotherapy was significantly associated with early mortality (p=0.003). Moreover, trastuzumab use was observed only in patients who survived beyond 6 months (p=0.011). No significant differences were observed regarding gender, smoking status, tumor location, tumor differentiation, Lauren classification, disease presentation, or presence of liver or lung metastasis (Table 1).

Comparison of Continuous Variables

The comparison of continuous variables between the groups is shown in Table 2. Patients who died within the first 6 months had significantly lower serum albumin levels (28.6±7.7 vs 36.7±5.6 g/L, p<0.001) and higher CRP levels (52.8±59.0 vs 23.1±32.5 mg/L, p=0.016). No statistically significant differences were observed for age, BMI, tumor markers (CEA, CA19-9, CA-125), LDH, WBC, hemoglobin, platelet count, neutrophil count, lymphocyte count, or monocyte count. (Table 2).

Table 2. Comparison of continuous variables according to six-month mortality

Variable	Survived beyond 6 months (n=62) mean±SD	Died within 6 months (n=29) mean±SD	p
Age	62.0±10.0	66.1±8.8	0.065
BMI	22.26±2.06	23.05±2.90	0.194
CEA	510.6±2186.9	96.6±298.4	0.173
CA19-9	607.5±1822.1	402.0±1233.0	0.544
CA-125	241.0±1337.3	203.5±274.4	0.852
LDH	321.9±359.3	395.4±353.8	0.406
Albumin	36.7±5.6	28.6±7.7	<0.001
CRP	23.1±32.5	52.8±59.0	0.016
WBC	8132±3571	10802±11808	0.243
Hemoglobin	11.99±2.02	11.16±1.78	0.053
Platelet	318,414±142,553	311,759±111,018	0.812
Neutrophil	5524±2947	8086±11335	0.241
Lymphocyte	3464±13447	1547±851	0.284
Monocyte	786±832	752±492	0.813

SD: Standard deviation, BMI: Body-mass index, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, CA-125: Cancer antigen 125, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cell, HB: Hemoglobin, PLT: Platelet, NEU: Neutrophil, LYM: Lymphocyte. Data are presented as mean±standard deviation. P values were calculated using the independent-samples t-test

Logistic Regression Analysis

Univariate logistic regression analysis demonstrated that response to first-line chemotherapy (odds ratio (OR) 2.40, 95% CI 1.42–4.06, p=0.001), serum albumin level (OR 0.84, 95% CI 0.77–0.92, p<0.001), and CRP level (OR 1.02, 95% CI 1.00–1.03, p=0.010) were significantly associated with six-month mortality. Other clinical and laboratory parameters were not significantly associated with early mortality.

In the univariate logistic regression analysis conducted to identify risk factors for early mortality, variables with p<0.10 (age, ECOG score, chemotherapy response, serum

albumin, and CRP) were included in the multivariable analysis. Trastuzumab use, which was found to be significant in the between-group comparison, was not included in the regression model because the OR could not be calculated mathematically, as it was observed only in the survival group. In the multivariable logistic regression analysis using the forward stepwise (LR) method, baseline serum albumin was the only variable that remained independently associated with six-month mortality (OR 0.84, 95% CI 0.77–0.92, p<0.001) (**Table 3**).

Table 3. Univariate and multivariable logistic regression analyses for predictors of six-month mortality

	Univariate analysis			Multivariable analysis		
Variables	**p value**	**OR**	**95% CI**	**p value**	**OR**	**95% CI**
Gender	0.722	0.84	0.32–2.20			
Age at diagnosis	0.065	1.05	0.99–1.10			
Comorbidity	0.122	2.56	0.78–8.40			
Weight loss	0.108	2.15	0.85–5.47			
Body-mass index	0.144	1.15	0.95–1.38			
ECOG ≥2	0.051	2.53	1.00–6.42			
Tumor location (cardia)	0.483	1.38	0.56–3.37			
Poor differentiation	0.140	1.96	0.80–4.80			
HER2 positivity	0.109	0.28	0.06–1.33			
Liver metastasis	0.909	1.05	0.43–2.56			
First-line chemotherapy regimen	0.773	1.06	0.73–1.54			
Response to first-line chemotherapy	0.001	2.40	1.42–4.06			
CEA(ng/ml)	0.429	1	0.99–1.00			
LDH(U/L)	0.410	1	0.99–1.00			
Platelet	0.824	1	1.00–1.00			
Neutrophil	0.219	1	1.00–1.00			
Lymphocyte	0.345	1	0.99–1.00			
Albumin(g/L)	<0.001	0.84	0.77–0.92	<0.001	0.84	0.77–0.92
C-reactive protein(mg/L)	0.010	1.02	1.00–1.03			

BMI: Body-mass index, ECOG: Eastern Cooperative Oncology Group performance status, HER2: Human epidermal growth factor receptor 2, CEA: Carcinoembryonic antigen, LDH: Lactate dehydrogenase, OR: Odds ratio, CI: Confidence interval.*Multivariate analysis was performed using forward stepwise logistic regression including variables with p<0.10 in univariate analysis

ROC Analysis

ROC curve analysis demonstrated that serum albumin had good predictive performance for six-month mortality, with an area under the curve (AUC) of 0.80 (95% CI 0.68–0.92, p<0.001). The optimal cut-off value for albumin was ≤35 g/L, which yielded a sensitivity of 80% and a specificity of 53% for predicting early mortality (**Table 4**) (**Figure**).

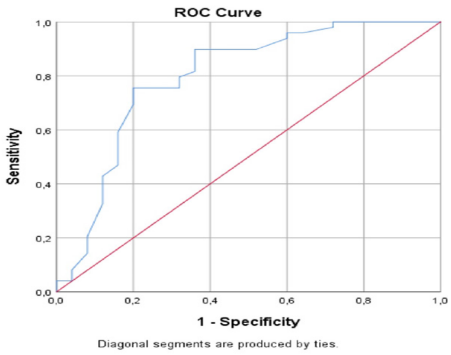


Figure. ROC analysis of serum albumin for prediction of 6-month mortality
ROC: Receiver operating characteristic

DISCUSSION

In our study, we investigated factors associated with six-month early mortality in patients with metastatic gastric cancer receiving systemic therapy. Mortality within the first six months was observed in 31.9% of the study population. In multivariable logistic regression analysis, baseline serum albumin remained independently associated with six-month mortality. ROC analysis demonstrated good discriminatory performance, with an AUC of 0.80. The identified cut-off value of ≤35 g/L yielded a sensitivity of 80% and a specificity of 53%. Although the relatively high sensitivity suggests potential usefulness for identifying patients at increased risk of early mortality, the modest specificity indicates that this threshold should not be used as a stand-alone clinical decision tool.

It has been shown that low albumin levels are associated with poorer survival in many types of cancer, particularly those of the GIT.[8] In a study conducted by Oñate-Ocaña and colleagues,[9] patients with gastric cancer were examined; the researchers noted that pre-treatment albumin levels are a strong prognostic factor and demonstrated that mortality increases as albumin levels decrease, alongside factors such as tumor stage (TNM), surgical resection, and type of lymphadenectomy. This finding is explained in a study by Almasaudi and colleagues on colorectal cancer not merely by simple nutritional deficiency but by increased systemic inflammation, disrupted body homeostasis, and the tumor's destructive power reducing the patient's physiological reserve.[10] In a study by Mao and colleagues,[11] it was emphasized that chronic inflammation suppresses albumin synthesis in the tumor microenvironment and that a decreased albumin-to-globulin ratio is a poor prognostic indicator in cancer patients. Consistent with previous literature, our findings indicate that lower pre-treatment serum albumin levels are associated with an increased risk of early mortality in patients with metastatic gastric cancer. This association may reflect the combined effects of systemic inflammation, nutritional impairment, and reduced physiological reserve.

Table 4. ROC analysis of serum albumin for prediction of six-month mortality

Variable	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	p value
Albumin	0.80 (0.68–0.92)	≤35 g/L	80	53	<0.001

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval

Although response to first-line chemotherapy was significantly associated with six-month mortality in the univariate analysis, it did not remain significant in the multivariable model, whereas baseline serum albumin remained independently associated with mortality. This finding suggests that baseline albumin may provide additional prognostic information beyond treatment response; however, this observation should be interpreted cautiously given the limited sample size and number of events.

Because serum albumin is inexpensive and routinely available, it may serve as a practical complementary marker when assessing the risk of early mortality alongside established clinical and disease-related factors.

Although our study demonstrates that low albumin levels are a poor prognostic factor for early mortality in patients with metastatic gastric cancer, there are studies in the literature that do not support this finding. In a study by Crumley et al.,[12] while serum albumin levels were associated with poor survival in univariate analysis in patients with gastric cancer, this association lost its statistical significance in multivariable analysis. In that study, low albumin levels were thought to be secondary to systemic inflammation. In our study, however, the association between low serum albumin levels and increased mortality can be attributed not only to systemic inflammation but also to malnutrition, cachexia, and reduced physiological reserves. Therefore, it should not be forgotten that albumin levels may decrease not only as a result of systemic inflammation but also due to factors that negatively affect survival, such as impaired nutritional status and reduced physiological reserves, and that this condition may increase mortality.

A study by McMillan[13] supports the view that hypoalbuminemia is not merely a result of nutritional deficiency, but also serves as a significant marker of tumor-induced inflammation and cachexia in cancer patients. It emphasized that the chronic systemic inflammatory response occurring in cancer patients is the most important driving force behind cancer cachexia. This study found that objective scoring systems, such as the Glasgow Prognostic Score, which evaluates serum albumin levels in conjunction with CRP, serve as important predictors of nutritional deterioration and worsening survival in patients.[13] In our study, although CRP was found to be associated with early mortality in univariate analysis, serum albumin remained the sole independent predictor in multivariable analysis. This finding can be explained by the fact that albumin and CRP are acute-phase reactants and are correlated with each other. Albumin is an acute-phase reactant synthesized in the liver; while it decreases in chronic inflammation, reduced protein intake and increased cytokines (particularly interleukin-6 and tumor necrosis factor-alpha) contribute to this decrease. The reason albumin is a superior predictor in multivariable analysis is that it serves not only as a marker of tumor-induced systemic inflammation but also reflects the patient's nutritional status and cachectic wasting. Albumin's longer half-life compared to CRP may have allowed it to more stably reflect the physiological depletion observed in metastatic gastric cancer.

A study by Zhang and colleagues[14] demonstrated that tumor markers such as serum carcinoembryonic antigen (CEA) and CA19-9 are insufficient for predicting survival in gastric cancer. The study investigated the impact of the Modified Glasgow Prognostic Score—derived from serum albumin and CRP levels—on prognosis in patients with normal tumor marker levels. It was found that even in advanced-stage patients, those with normal tumor markers but low albumin levels had a poor prognosis for survival.[14] In our study, focusing on serum albumin in metastatic gastric cancer, we found that serum albumin showed good discriminatory ability for six-month early mortality, which supports the findings of Zhang and colleagues.[14] In advanced-stage patients, where tumor markers may not fully predict clinical course, even a low-cost serum albumin test alone is significant in determining the risk of early mortality. This suggests that the readily accessible serum albumin test may be more reliable than tumor markers in the clinical decision-making process.

A review of the literature on gastric cancer studies has shown that elevated serum CEA and CA19-9 levels are independent risk factors for poor survival.[15,16] In our study, no statistically significant difference was found in CEA (p=0.173) and CA19-9 (p=0.544) levels between patients who died within 6 months and those who survived. Similarly, studies have shown that laboratory values such as neutrophil, lymphocyte, and platelet counts—specifically the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio—have a poor prognostic effect on survival in gastric cancer.[17,18] In our study, however, these blood cell values (neutrophils p=0.241, lymphocytes p=0.284, platelets p=0.812) were found to lack statistical significance in predicting early mortality. Upon clinical and pathological examination, it was determined that poor tumor differentiation and the presence of liver metastases are factors that dramatically affect the patient's prognosis and significantly reduce survival.[19] In our study, however, major prognostic factors such as tumor differentiation grade (p=0.137) and the presence of liver metastases (p=0.909) did not result in differences between the six-month survival groups. The reason for this discrepancy may be that previous studies often included heterogeneous disease stages and evaluated long-term survival, whereas our study focused exclusively on patients with metastatic gastric cancer, including both de novo and recurrent metastatic disease, and evaluated short-term six-month mortality. Frail patients in the terminal stage of metastatic disease are influenced more by the patient's physiological reserve, malnutrition status, and systemic inflammation than by the location of the metastasis or the tumor's histological characteristics.

Limitations

The single-center and retrospective nature of our study are among its main limitations. In addition, the relatively small sample size and limited number of early mortality events should be considered when interpreting the multivariable analysis. Specifically, 29 early mortality events were observed, and five candidate variables were entered into the multivariable modeling process, corresponding to approximately 5.8 events per variable. This value is below the conventionally suggested threshold of 10 events per variable and may increase the risk of model overfitting and instability of the estimated associations. Furthermore, residual confounding due to unmeasured variables cannot be excluded, and detailed nutritional assessment tools or

dietary questionnaires were not available. Despite all these limitations, our study has demonstrated the prognostic significance of serum albumin levels, a test that is easily accessible and low-cost in clinical practice. The fact that a critical factor such as "response to first-line chemotherapy"—which was significant in univariate analysis—yields to serum albumin levels in multivariable analysis highlights just how important this parameter is. The finding that serum albumin is more reliable than tumor markers in predicting pre-treatment clinical course in patients with advanced gastric cancer will serve as a guide for developing supportive care strategies for albumin in clinical practice.

CONCLUSION

Pre-treatment serum albumin was independently associated with six-month mortality in patients with metastatic gastric cancer and may represent an accessible and potentially useful prognostic marker. Although an albumin level of ≤35 g/L demonstrated good overall discrimination and relatively high sensitivity, its modest specificity limits its use as a stand-alone predictor. Serum albumin may therefore complement clinical assessment when identifying patients at increased risk of early mortality. Prospective multicenter studies and external validation cohorts are needed to confirm these findings and validate the proposed cut-off.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Clinical Researches Ethics Committee at the Van Yüzüncü Yıl University (Date: 17.04.2026, Decision No: 2026/04-04).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: MK, MÜ; Design: MK; Control: MÜ; Resources: MK; Materials: MK, MÜ; Data Collection and/or Processing: MÜ; Analysis and/or Interpretation: MK; Literature Review: MÜ; Writing the Article: MK; Critical Review: MK, MÜ.

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Original Article

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Clinical characteristics, treatment outcomes, and survival of primary bone diffuse large B-cell lymphoma: a descriptive single-center retrospective study

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ABSTRACT

Aims: Primary bone diffuse large B-cell lymphoma (PB-DLBCL) is a rare extranodal lymphoma with generally favorable outcomes following anthracycline-based immunochemotherapy. Data on the clinical characteristics and outcomes of unifocal (UF) and multifocal (MF) disease remain limited. This study aimed to describe the clinical characteristics, treatment outcomes, survival, and safety of patients with PB-DLBCL and to present descriptive comparisons between UF and MF disease.

Methods: This retrospective single-center study included 13 consecutive adult patients with histologically confirmed PB-DLBCL diagnosed between 2010 and 2025. Patients were classified as UF (n=9) or MF (n=4) according to the number of involved bone sites. Clinical characteristics, treatment response, survival outcomes, and treatment-related adverse events were evaluated.

Results: The median age was 60 years (range, 18–78), and localized bone pain was the most common presenting symptom (92.3%). Patients with MF disease showed a higher frequency of adverse clinical characteristics, including bulky lesions, elevated lactate dehydrogenase levels, larger lesions, and poorer performance status. Complete and partial responses were achieved in 9 patients (69.2%) and 1 patient (7.7%), respectively, yielding an overall response rate of 76.9%. The overall response rate was 100% in the UF group and 25% in the MF group (p=0.014). The median overall survival (OS) was 88.15 months, with a 2-year OS rate of 91.7%. The 2-year OS rates were 100% in the UF group and 66.7% in the MF group. Hematologic toxicities were the most common adverse events, while grade 3–4 toxicities were infrequent and treatment was generally well tolerated.

Conclusion: Anthracycline-based immunochemotherapy was associated with favorable treatment responses and survival outcomes in our cohort. Patients with MF disease showed lower response rates and survival than those with UF disease; however, given the small and imbalanced subgroup sizes, these findings should be interpreted with caution. The outcomes observed in patients with MF disease should be further evaluated in larger cohorts, and prospective studies are needed to identify more effective treatment strategies for this subgroup.

Keywords: Lymphoma; bone neoplasms, diffuse large B-cell lymphoma, treatment outcome

INTRODUCTION

Primary bone lymphoma (PBL) is a neoplasm composed of malignant lymphoid cells that presents with solitary or multiple bone lesions with or without nodal involvement and must be distinguished from the secondary bone involvement of systemic lymphomas.[1] Bone involvement is not uncommon in advanced-stage lymphoma originating in other sites, but PBL is a rare entity. It accounts for approximately 3–7% of malignant bone tumors, nearly 5% of all extranodal lymphomas, and about 1% of non-Hodgkin lymphomas.[2,3] While PBL can present at any age, its peak incidence typically occurs within the fifth and 6th decades with a slight male predilection.[1]

The most common presenting symptoms of PBL are localized bone pain and a palpable mass; it may be complicated by pathological fracture or spinal cord compression at presentation. However, systemic 'B' symptoms, namely fever, night sweats and weight loss are less frequently observed, typically occurring in less than 10% of cases.[2,3] While most patients are presented with localized (limited-stage) disease,

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advanced-stage involvement is also reported in the literature.[4] PBL can develop throughout the entire skeleton; however, it shows a predilection for long bones (specifically the femur, tibia, and humerus), and axial skeletal sites such as the pelvis and spine.[5]

Although various subtypes, including B-cell, T-cell, and Hodgkin lymphoma, can present as PBL, the most common histological subtype is diffuse large B-cell lymphoma (DLBCL)[2,3] and it should be differentiated from other bone tumors including osteosarcoma, Ewing sarcoma, or chronic osteomyelitis. Despite advancements in imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT), definitive diagnosis remains challenging and depended on histopathological examination and immunohistochemical staining.

Due to the rarity of the disease and the lack of large-scale randomized controlled trials, a definitive treatment standard for PBL has not yet been established. While management historically relied on radiotherapy (RT), in the rituximab era, the cornerstone of treatment has shifted to anthracycline-based chemoimmunotherapy, namely R-CHOP. Although RT still maintains its clinical relevance, it is now primarily used as a consolidative therapy for preventing local relapses. surgery is reserved for diagnostic purposes or symptom management in a limited group of patients with specific complications.[6,7]

In this study, we aimed to describe the clinical characteristics, diagnostic findings, treatment responses, and survival outcomes of 13 patients diagnosed with PBL at our tertiary care center. By sharing our institutional experience, we aim to contribute to the literature on this rare entity and discuss our findings in the light of current management strategies.

METHODS

Ethics

This study was approved by the Non-interventional Clinical Researches Ethics Committee of Marmara University Faculty of Medicine (Date: 27.03.2026, Decision No: 09.2026.26-0369). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

This retrospective study included patients aged ≥18 years who were diagnosed with PBL between 2010 and 2025 at our institution. PBL was defined as lymphoma involving a single bone site with or without regional lymph node involvement, or lymphoma involving multiple bones without evidence of visceral or bone marrow involvement.[3,6] All the patients had a histopathologically confirmed diagnosis of DLBCL. Diagnostic tissue sampling was obtained by excisional biopsy in 5 patients (38.5%) and by tru-cut biopsy in 8 patients (61.5%). Among the patients, 6 (46.2%) were classified as germinal center B-cell subtype, whereas 5 (38.5%) were classified as non-germinal center subtype. In 2 patients (15.4%), the subtype was not specified. Patients with systemic lymphoma and secondary bone involvement, those younger than 18 years of age, and those with incomplete data were excluded. Patients diagnosed with Hodgkin lymphoma and non–Hodgkin lymphoma subtypes other than DLBCL (including T-cell lymphomas and indolent B-cell lymphomas) were also excluded from the study group. Clinical data, including age, gender, presenting symptoms, involved bone sites, stage at diagnosis, International Prognostic Index (IPI) score, Eastern Cooperative Oncology Group (ECOG) performance status, laboratory parameters (LDH, hemoglobin, etc.), treatment regimens, and outcomes were extracted from medical records. Bulky lesion was defined as a tumor mass measuring ≥7.5 cm in the largest diameter.[8]

The patients were subcategorized as multifocal (MF) or unifocal (UF) disease, according to the number of bone sites involved. The involvement of only one site was defined as unifocal disease (UF), whereas the involvement of two or more sites was defined as multifocal disease (MF).

Staging

All patients underwent staging at diagnosis using PET/CT. Bone marrow biopsy was performed in all patients and none of the patients had bone marrow involvement. Disease staging was assessed according to the Ann Arbor Staging System.[9] Patients with disease confined to a single bone site were categorized as stage IE, while those with regional lymph node involvement were categorized as stage IIE. Stage IV was defined as multiple bone involvement without evidence of distant nodal or visceral disease. Stage IIIE patients, defined as those with distant nodal disease and patients with extranodal involvement other than bone were excluded from the definition of PBL.

Treatment Characteristics and Follow up

All of the patients except one patient were treated with RCHOP regimen for 6 cycles every 21 days (rituximab 375mg/m^2, day 1; cyclophosphamide 750 mg/m^2, day 1; doxorubicin 50 mg/m^2, day1; vincristine 1.4 mg/m^2 (capping the dose at 2 mg) day 1; prednisolone 40 mg/m^2 day 1-5). One patient was treated with R-CEOP therapy (rituximab 375mg/m^2, day 1; cyclophosphamide 750 mg/m^2, day 1; etoposide 50 mg/m^2, day1; vincristine 1.4 mg/m^2 (capping the dose at 2 mg) day 1; prednisolone 40 mg/m^2, day 1-5) for six cycles. R-CEOP was preferred due to low ejection fraction ratio of 35% in that patient. RT was administered in addition to chemotherapy in two patients with a bulky disease and pathological fracture.

BR (Rituximab 375 mg/m^2 day 1; bendamustine 90 mg/m^2 day 1 and 2) and R- ICE (rituximab 375 mg/m^2 day 1; etoposide 100mg/m^2 day 1-3; carboplatin AUC 5× (glomerular filtration rate+25) mg [capping the dose at 800 mg]; ifosfamide 5000mg/m^2) therapy were preferred as salvage therapy and autologous stem cell transplantation (ASCT) was performed in eligible patients.

Supportive care measures, including granulocyte colony-stimulating factor (G-CSF) and mesna prophylaxis, were provided in accordance with institutional protocols.

All patients underwent PET-CT at diagnosis, after three cycles of treatment, and one month following completion of therapy. For patients receiving RT, post-treatment response assessment by PET-CT was performed 3 months after the

end of RT. Response to treatment was reported according to revised response criteria.[10] Overall survival (OS) was defined as the period from the date of PBL diagnosis to the date of the last follow-up visit, or the date of death from any cause.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics v20.0 (IBM Corp., Armonk, NY, USA). Data normality was confirmed via Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were expressed as medians (range) and compared using the Mann-Whitney U test or Student's t-test as appropriate. Categorical variables were analyzed using Fisher's exact test, whereas the Fisher–Freeman–Halton exact test was applied for categorical variables with more than two categories. Survival outcomes were estimated using the Kaplan-Meier method.

RESULTS

Patients' Characteristics

Thirteen patients with PBL were included in the study. The median age was 60 (range, 18-78). Six patients (46.2%) were male and seven patients were female (53.8%) with a female to male ratio of 1.16. Although this difference did not reach statistical significance, male patients constituted a higher proportion of the MF group than of the UF group (75% vs. 33.3%). The characteristics of each patient were reported in **Supplementary Table 1**.

Patients most frequently presented with pain localized to the involved bone, which was observed in 12 patients (92.3%). Other presenting manifestations included swelling in five patients (38.5%), B symptoms in one patient, pathological fracture in one patient (7.7%), and compression-related neurological manifestations in one patient (7.7%).

Among nine patients with UF, craniofacial bones and long bones were the most frequently involved sites, each accounting for 33.3% of cases. Among the four patients with MF, vertebral involvement was the predominant site of disease, occurring in three patients (75.0%), followed by rib involvement in two patients (50.0%). The sites of involvement for each patient were detailed in **Supplementary Table 1**.

At initial diagnosis, 4 patients (30.8%) had stage IE disease, 5 (38.5%) had stage IIE disease, and 4 (30.8%) had stage IV disease. Among the patients with stage IV disease, only one presented with B symptoms and was therefore classified as stage IVB. Four patients were categorized as MF disease and 9 patients were documented as UF disease. The characteristics of the patients with UF and MF disease at the time of diagnosis were summarized at **Table 1**.

Evaluation of laboratory parameters at diagnosis revealed that the median LDH level, white blood cell count, hemoglobin level, and platelet count were 217 IU/l (range, 136-702), 7×10^9/L (range, 4.5-13×109/l), 12.4 gr/dl (range, 9.9-15.8) and 280×10^9/L (range, 160-480×109/l), respectively. The laboratory tests of the patients at the time of diagnosis were summarized at **Table 1**.

Patients with MF disease also tended to present with more adverse clinical characteristics, including a higher frequency of bulky lesions (50% vs. 11.1%), B symptoms (25% vs. 0%), and elevated LDH levels (75% vs. 33.3%). In addition, the MF group had a larger median index lesion size (80 vs. 25 mm), higher median LDH levels (370 vs. 217 IU/l), and a slightly poorer ECOG performance status (median ECOG score: 1 vs. 0).

Clinical Outcomes and Survival Data of the Patients

CR and PR were achieved in 9 (69.2%) patients and one (7.7%) patient, respectively, resulting in an overall response rate of 76.9%. Three patients (23.1 %) had refractory disease following first-line therapy; all refractory patients had MF disease at diagnosis. Patient with PR was consolidated with RT and achieved CR after RT. No patients with CR or PR had relapsed after median 55 months (range, 20-126). The response rates were summarized in patients with MF and UF diseases in **Table 2** and **Supplementary Table 1**. The overall response rate (CR+PR) was 100% in patients with UF disease, whereas only one patient (25%) with MF disease achieved an overall response (p=0.014).

Three patients had refractory disease and received salvage therapy with BR or R-ICE. Following second-line treatment, two patients achieved PR and one patient achieved CR. One

Supplementary Table 1. Characteristics of the patients

Patients no	Age	Gender	ECOG	Bulky lesion	B symptoms	Site of involvement	Staging	UF/MF	Response to first treatment
1	35	F	0	No	No	Maxilla	1	UF	CR
2	56	M	0	No	No	Iliac bone	2	UF	CR
3	59	M	0	No	No	Maxilla	2	UF	CR
4	60	F	0	No	No	Femur	2	UF	CR
5	65	M	1	Yes	No	Mandibula	1	UF	CR
6	66	F	1	No	No	Femur	2	UF	CR
7	68	F	0	No	No	Xiphoid process	2	UF	CR
8	68	F	0	No	No	Humerus	1	UF	CR
9	70	F	1	No	No	Iliac bone	1	UF	PR
10	18	F	0	No	No	Multiple vertebra involvement	4	MF	CR
11	58	M	1	Yes	No	vertebra, rib, femur, acetabulum	4	MF	RD
12	60	M	1	No	No	Multiple vertebra involvement	4	MF	RD
13	78	M	2	Yes	Yes	Scapula, rib, ischium	4	MF	RD

ECOG: Eastern Cooperative Oncology Group, MF: Multifocal disease, F: Female, UF: Unifocal disease, CR: Complete response, M: Male, PR: Partial response, RD: Refractory disease.

Table 1. Characteristics and laboratory results of the patients at diagnosis

	All	Unifocal disease	Multifocal disease	P value
Number	13	9 (69.2)	4 (30.8)	
Age (median, range)	60 (18-78)	65 (35-70)	59 (18-78)	0.64
Gender (number, %) Female Male	 7 (53.8) 6 (46.2)	 6 (66.7) 3 (33.3)	 1 (25) 3 (75)	0.27
ECOG (median, range)	1 (0-2)	0 (0-1)	1 (0-2)	0.14
ECOG (number, %) 0/1 2	 12 (92) 1 (7.8)	 9 (100) -	 3 (75) 1 (25)	0.31
IPI (median, range)	2 (0-4)	2 (0-4)	2 (0-3)	0.3
Size of the index lesion (mm) (median, range)	32 (21-110)	25 (21-84)	80 (35-110)	0.67
Bulky lesion (number, %) Yes No	 3 (23) 10 (77)	 1 (11.1) 8 (88.9)	 2 (50) 2(50)	0.20
B symptoms (number, %) Yes No	 1 (7.8) 12 (92.2)	 - 9 (100)	 1 (25) 3 (75)	0.31
Staging (number, %) Stage 1 Stage 2 Stage 4	 4 (30.8) 5 (38.4) 4 (30.8)	 4 (44.4) 5 (55.6) -	 - - 4 (100)	0.003
LDH (IU/l) (median, range)	217 (136-702)	217 (136-702)	370 (190-690)	0.32
LDH (number, %) High Low	 6 (46.2) 7 (53.8)	 3 (33) 6 (66.7)	 3 (75) 1 (25)	0.27
WBC at the time of diagnosis (median, range) ($\times 10^9$/l)	7 (4.5-13)	6.9 (4.5-13)	9.2 (7.2-9.6)	0.40
Lymphocyte at the time of diagnosis (median, range) ($\times 10^9$/l)	1.5(0.6-2.5)	1.5 (0.6-2.5)	1.6 (1.1-2.5)	0.76
Platelet at the time of diagnosis (median, range) ($\times 10^9$/l)	280 (160-480)	270 (175-420)	354 (160-480)	1
Neutrophil at the time of diagnosis (median, range) ($\times 10^9$/l)	4.2 (2.6-9.2)	4.8 (2.6-9.2)	3.5 (2.7-6.8)	0.71
Hemoglobin at the time of diagnosis (median, range) (gr/dl)	12.4 (9.9-15.8)	12.2 (9.9-15.8)	11.7 (11-12.6)	0.54

ECOG: Eastern Cooperative Oncology Group, IPI: International Prognostic Index, LDH: Lactate dehydrogenase, WBC: White blood cell.

Table 2. Response rates of the patients to the first line therapy

Response to first line therapy	All patients (n=13) (n, %)	UF (n=9) (n, %)	MF (n=4) (n, %)	P value
CR PR RD	9 (69.2) 1 (7.8) 3 (23)	8(88.9) 1 (11.1) -	1 (25) - 3 (75)	p=0.0121

UF: Unifocal disease, MF: Multifocal disease, CR: Complete response, PR: Partial response, RD: Refractory disease

patient who achieved PR was not eligible for ASCT because of advanced age and poor ECOG performance status. This patient relapsed 6 months after completing six cycles of BR. The second patient, who achieved PR, proceeded to ASCT and the patient relapsed after 24 months.

The third patient achieved CR with salvage therapy and subsequently underwent ASCT while in CR. This patient has remained in remission following transplantation.

The median OS for the entire cohort was 88.15 months, with a 2-year OS rate of 91.67%. The 2-year OS rate was 100% in patients with UF disease and 66.67% in those with MF disease (**Figures 1 and 2**).

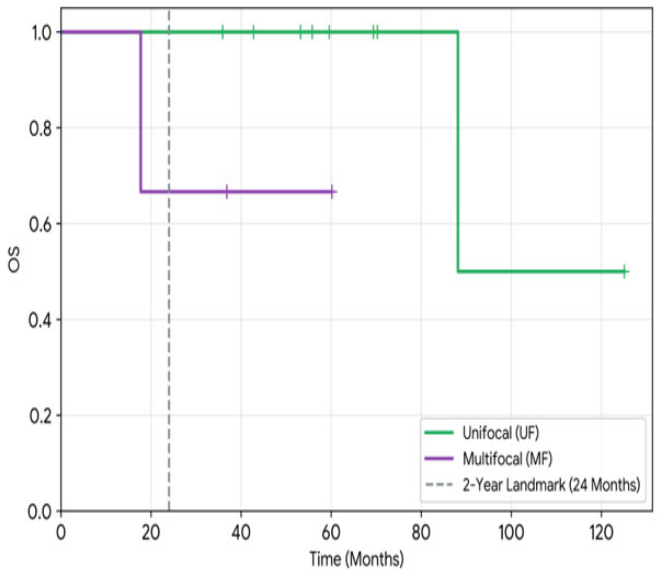


Figure 1. The overall survival of patients with unifocal and multifocal disease.
OS: Overall survival, UF: Unifocal, MF : Multifocal

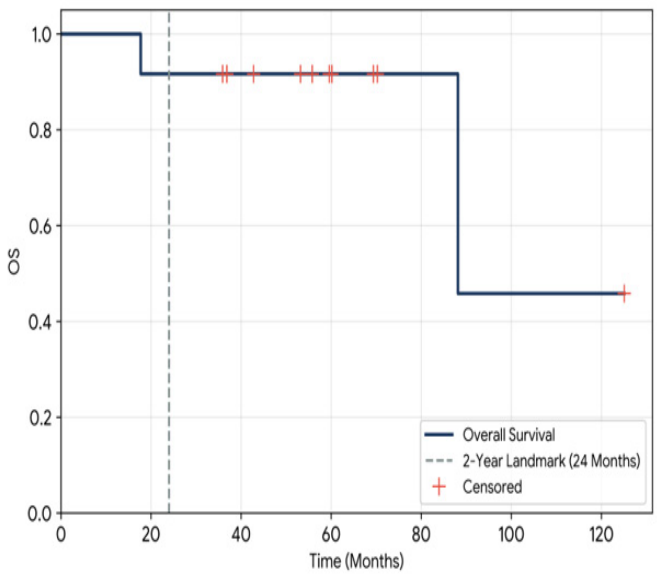


Figure 2. The overall survival of all cohort.
OS: Overall survival

During the follow-up period, two patients died. One patient in the MF group died due to refractory disease and subsequent infectious complications. One patient in the UF group died while in remission; however, the cause of death could not be determined.

Safety Data

Overall, 11 of 13 patients (84.6%) experienced at least one adverse event of any grade, while grade 3–4 adverse events were observed in 3 patients (23.1%). The most common adverse events were anemia and neutropenia, each occurring in 11 patients. All cases of anemia were grade 1–2, whereas neutropenia was grade 1–2 in 8 patients and grade 3–4 in 3 patients. Thrombocytopenia was observed in 3 patients and was limited to grade 1–2. Febrile neutropenia occurred in 3 patients. Non-hematologic adverse events included mucositis in 4 patients and peripheral neuropathy in 2 patients; all cases of neuropathy were grade 1.

R-CHOP therapy was delayed in four patients (33.3%). The delay occurred once in two patients and twice in two patients, with a median duration of 12 days (range, 7–15 days). The causes for therapy delay were urinary tract infection and pneumonia in two patients and neutropenia in two patients. R-CEOP treatment was delayed during the first two cycles because of neutropenia. After prophylactic granulocyte stimulating agent (G-CSF) was incorporated into the treatment regimen, all subsequent cycles were delivered on time without further delays or interruptions. No dose reductions or other dose modifications were necessary.

DISCUSSION

PBL is a rare extranodal lymphoma, and the limited number of reported cases continues to challenge the establishment of standardized management strategies. In the present study, we evaluated the clinical characteristics, treatment outcomes, and survival of 13 patients with DLBCL-type PBL treated at a single tertiary center.

The median age of our cohort was 60 years (range, 18–78), which is consistent with previous retrospective studies reporting a median age between 45 and 65 years.[3,7,11] Similar to earlier reports, our patients showed a broad age distribution at diagnosis. In the literature, PBL has been reported in adults ranging from 18 to 87 years of age. Therefore, while the disease is most frequently diagnosed in middle-aged and older adults, it may present at almost any adult age. The age distribution and median age in our cohort were similar not only to those reported in previous PBL series but also to those observed in DLBCL patients.[12]

Although females accounted for 53.8% of patients in our cohort, previous studies have generally reported a slight male predominance in PBL.[3,5] This discrepancy is likely related to the small sample size. Males represented 75% of patients with MF disease, whereas females were more common in the UF group. However, given the small number of patients with MF disease, this difference should be interpreted with caution.

Most patients in our cohort presented with localized symptoms, such as pain and swelling, while B symptoms were uncommon at presentation. Similarly, previous studies have shown that local bone pain is the most common presenting symptom, occurring in approximately 80–95% of patients, whereas B symptoms are reported in only 4–12% of cases.[7,11,13-15] In our study, none of the patients with UF PBL had B symptoms, whereas only one patient (25%) with MF disease presented with constitutional symptoms. This finding was partly consistent with the study by Ayesh Haj Yousef et al.,[11] who also reported no B symptoms among patients with UF disease, although B symptoms were present in 75% of patients with MF disease. The discrepancy in the frequency of B symptoms among patients with MF disease may be explained by the small sample sizes and retrospective design of both studies. In a large population-based cohort of patients with DLBCL, the incidence of B symptoms increased from 16.4% in Ann Arbor stage I to 40.9% in stage IV disease.[12] In contrast, B symptoms remained uncommon in our cohort, even among patients with stage IV disease. Although sample sizes were limited in both studies, these findings might suggest that constitutional symptoms in primary bone DLBCL are highly variable, even in advanced-stage disease. Therefore, the presence or absence of B symptoms alone has limited diagnostic value and should not be relied upon to establish or exclude the diagnosis of primary bone DLBCL.

Our analysis demonstrated distinct patterns of skeletal involvement according to disease extent, with craniofacial and long bones being the most commonly affected sites in UF disease and vertebral lesions predominating in MF disease. These findings are in line with previous studies reporting the femur as one of the most frequently involved bones in PBL and highlighting the axial skeleton, particularly the vertebrae and pelvis, as preferential sites of MF disease.[11,16-18]

In our study, the median IPI score was 2 in both the UF and MF groups, and the distribution of IPI scores was similar between the two subgroups. ECOG performance status was generally favorable, with only one patient in the MF group having an ECOG score of 2. In contrast, Sharma et al.[16] reported ECOG scores ≥2 in nearly one-third of patients. This difference may be explained by the higher tumor burden in their cohort, which included a greater proportion of patients with stage IV disease, B symptoms, elevated LDH levels, and higher IPI scores.

Patients with MF disease showed a higher frequency of adverse clinical characteristics, including bulky lesions, B symptoms, elevated LDH levels, larger bone lesions, and poorer performance status. Similar clinical patterns have been reported in previous studies.[3,11,19]

The results in our study revealed that hematological laboratory parameters were generally within normal ranges at diagnosis. This observation highlights that complete blood count findings may be non-specific and insufficient to prompt the diagnosis of PBL. Consequently, normal hematological parameters should not exclude further investigation in patients with clinically or radiologically suspicious bone lesions.

In our cohort, all patients with UF disease achieved an overall response (100%), whereas one patient (25%) with MF disease responded to first-line treatment. The 2-year OS rates were 100% in the UF group and 66.67% in the MF group. Given the small number of patients, particularly in the MF group, these differences between MF and UF groups should be interpreted with caution. Previous studies have reported excellent overall response rates of approximately 85–90% in patients with primary bone DLBCL treated with anthracycline-based immunochemotherapy, with or without

consolidative RT.[3,6,16] However, data comparing outcomes according to disease distribution remain limited. Consistent with our findings, Ayesh et al.[11] reported that no patient with MF achieved a complete response, whereas only one patient with UF failed to achieve CR, corresponding to a CR rate of 87.5% in the UF group. Similarly, Wu et al.[19] demonstrated significantly superior survival among patients with localized disease, reporting a 5-year OS of 83.4% in the UF group compared with 36.7% in the MF group. Likewise, Rezazadeh et al.[7] reported excellent long-term outcomes in patients with limited-stage primary bone DLBCL, with a 10-year OS approaching 80–90%. Overall, while PB-DLBCL is generally associated with favorable treatment responses and survival outcomes, the inferior outcomes observed in patients with MF disease should be further evaluated in larger cohorts. Prospective studies are needed to identify more effective treatment strategies for patients with MF disease to increase response rates and survival.

The safety profile observed in our cohort was comparable to that reported in previous studies of R-CHOP–based therapy, in which hematologic toxicities, particularly neutropenia and febrile neutropenia, are among the most common treatment-related adverse events.[20-22] In our cohort, grade 3–4 adverse events were infrequent, and treatment delays were limited, occurring mainly because of neutropenia or infection. The introduction of prophylactic G-CSF in patients who developed neutropenia prevented further treatment delays, allowing all subsequent treatment cycles to be administered on schedule. Overall, R-CHOP–based immunochemotherapy was generally well tolerated, and no patient required dose reduction or treatment discontinuation because of treatment-related toxicity.

Limitations

This study had several limitations. First, its retrospective design may have resulted in information bias. Second, the study included a relatively small number of patients from a single tertiary center, reflecting the rarity of PBL and limiting the statistical power and generalizability of our findings. Given the small and imbalanced subgroup sizes, the statistical comparisons and associated p-values between UF and MF disease should be interpreted with caution. In addition, the small sample size precluded multivariable analyses to identify independent prognostic factors. Nevertheless, despite these limitations, our study provides detailed clinical, treatment, and survival data on this rare disease and adds to the limited real-world evidence on PB-DLBCL with UF and MF involvement. Larger multicenter studies are needed to validate these observed differences and more reliably assess their clinical and prognostic significance.

CONCLUSION

As a result, PB-DLBCL treated with anthracycline-based immunochemotherapy demonstrated favorable treatment responses and survival outcomes in our cohort. Patients with MF disease showed lower response rates and survival than those with UF disease; however, given the small and imbalanced subgroup sizes, these findings should be interpreted with caution. The inclusion of only PBL cases with DLBCL histology resulted in a clinically homogeneous study population. The outcomes observed in patients with MF disease should be further evaluated in larger cohorts. Prospective studies are needed to identify more effective treatment strategies for patients with MF disease.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Clinical Researches Ethics Committee of Marmara University Faculty of Medicine (Date: 27.03.2026, Decision No: 09.2026.26-0369).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: AFY, IA; Design: MUM, TT; Control: ES, SÖ, FA; Resources: TE, AB; Materials: RBÖ, CG; Data Collection and/or Processing: FT, AFY; Analysis and/or Interpretation: AFY, IA; Literature Review: TT, FA; Writing the Article: AFY; Critical Review: AFY, MUM, TE, AB, RBÖ, CG, SÖ, FT, FA, ES, TT, IA.

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Original Article

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Association of FISH cytogenetic risk and baseline PET/CT findings with early treatment response and disease progression in patients with newly diagnosed multiple myeloma

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ABSTRACT

Aims: To evaluate the association of fluorescence in situ hybridization (FISH)-defined cytogenetic risk and baseline positron emission tomography/ computed tomography (PET/CT) findings with early treatment response and early disease progression in patients with newly diagnosed multiple myeloma (MM).

Methods: Seventy patients with newly diagnosed MM were included in this retrospective study. Clinical characteristics, International Staging System (ISS) and Revised ISS (R-ISS) stage, lactate dehydrogenase (LDH) level, FISH-defined cytogenetic risk, and baseline PET/CT parameters, including the number of focal lesions, maximum standardized uptake value (SUV max), extramedullary disease, bone marrow involvement, and metabolic risk group, were recorded. Treatment responses after the second and fourth cycles were evaluated. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method, and exploratory associations with PFS were assessed using Cox proportional hazards regression.

Results: According to baseline PET/CT, 81.4% of patients were classified as having a metabolically high-risk disease. Compared with the metabolically low-risk group, patients in the metabolically high-risk group achieved significantly higher rates of very good partial response (VGPR) after the second cycle (49.1% vs. 15.4%, p=0.032) and ≥VGPR after the fourth cycle (64.9% vs. 23.1%, p=0.011). However, progression rates did not differ significantly between the two groups (p=0.675). Although response rates and progression frequency were numerically higher in the FISH high-risk group, these differences did not reach statistical significance. Kaplan–Meier analysis demonstrated longer PFS in female patients (p=0.001); ≥VGPR after the fourth cycle was not significantly associated with PFS (p=0.116). In the multivariable Cox model (13 PFS events), female gender remained significantly associated with PFS (HR=0.067, 95% CI 0.008–0.569, p=0.013), although the estimate was unstable because of the very limited number of events. The 1-year PFS and OS rates were 86% and 92%, respectively.

Conclusion: In this exploratory cohort, the study-specific PET/CT metabolic risk classification was associated with deeper early treatment responses but not with short-term disease progression. FISH-defined cytogenetic risk was not significantly associated with early response or progression. Given the short follow-up duration, limited number of events, and lack of external validation of the metabolic risk classification, these findings should be considered preliminary and do not establish the independent prognostic value of PET/CT or FISH-defined risk.

Keywords: Multiple myeloma, PET/CT, in situ hybridization; fluorescence, progression-free survival, treatment outcome

INTRODUCTION

Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal expansion of abnormal plasma cells within the bone marrow, resulting in monoclonal immunoglobulin production and progressive end-organ damage. Representing approximately 10% of hematologic malignancies, MM predominantly affects older individuals, with a median age at diagnosis of approximately 65–70 years.[1,2] MM is a biologically heterogeneous disease, and cytogenetic and molecular abnormalities are among the most important determinants of prognosis. Fluorescence in situ hybridization (FISH) is routinely used to identify recurrent high-risk chromosomal abnormalities; however, patients with similar cytogenetic profiles may still experience markedly different clinical outcomes, indicating that additional prognostic markers are required.

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Beyond cytogenetic evaluation, functional imaging has become an important component of the initial assessment of patients with MM. Among available imaging modalities, 18F-FDG PET/CT provides valuable information regarding tumor metabolic activity and disease distribution. Baseline PET/CT findings, including a high number of focal lesions, elevated SUVmax, and extramedullary disease, have been associated with adverse clinical outcomes. Previous studies have identified prognostically relevant SUVmax thresholds ranging from approximately 3.9 to 4.2. In addition, diffuse or mixed bone marrow FDG uptake patterns have been reported to be associated with inferior progression-free and overall survival (OS). However, the optimal combination of these parameters and their cutoff values has not been universally standardized. Consequently, PET/CT has emerged not only as a staging tool but also as a potential biomarker of disease burden and biological aggressiveness.[3-9]

Depth of response following induction therapy has also emerged as an important prognostic marker in patients with newly diagnosed MM. Several studies have demonstrated that achieving a very good partial response (VGPR) or better after induction therapy is associated with prolonged progression-free survival (PFS) and OS.[10]

Although both cytogenetic abnormalities and PET/CT findings have individually demonstrated prognostic value, evidence regarding their combined contribution to predicting early treatment response and disease progression remains limited. A better understanding of how these complementary risk assessment tools interact may improve early risk stratification and support individualized treatment strategies. Therefore, the present study aimed to investigate the relationship between FISH-defined cytogenetic risk, baseline 18F-FDG PET/CT findings, early treatment response, and short-term disease progression in patients with newly diagnosed MM.

METHODS

This study was approved by the Non-interventional Ethics Committee of İzmir City Hospital (Date: 29.04.2026, Decision No: 2026/280). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective, single-center study included patients newly diagnosed with MM at tertiary referral center, between December 2023 and October 2025. The data cut-off date for follow-up and survival analyses was May 15, 2026. Only patients who underwent both FISH cytogenetic analysis and baseline 18F-FDG PET/CT at diagnosis were eligible for inclusion. The diagnosis of MM was established according to the International Myeloma Working Group (IMWG) criteria.

Patients without baseline PET/CT imaging, unavailable FISH cytogenetic results, or incomplete early treatment response data were excluded.

Demographic characteristics, myeloma subtype, International Staging System (ISS) stage, Revised International Staging System (R-ISS) stage, serum lactate dehydrogenase (LDH) level, FISH cytogenetic findings, treatment regimens, autologous stem cell transplantation (ASCT) status, treatment responses, and follow-up data were retrospectively retrieved from the institutional electronic medical records. Serum LDH levels above the institutional upper limit of normal (233 U/L) were considered elevated. Treatment responses were assessed according to the IMWG response criteria. Responses after the second and fourth cycles of induction therapy were recorded. Achievement of a VGPR or better (≥VGPR) after the fourth cycle was defined as an early deep response. Disease progression included all progression events documented during the follow-up period.

FISH analysis was performed on unselected bone marrow aspirate samples obtained at diagnosis, without CD138-positive plasma cell enrichment. Patients harboring any of the following cytogenetic abnormalities were classified as having high-risk cytogenetics: del(17p), t(4;14), t(14;16), deletion 1p, and/or gain of chromosome 1q. Patients without these abnormalities were classified as having standard-risk cytogenetics.

Baseline 18F-FDG PET/CT was performed in all patients at diagnosis and interpreted by experienced nuclear medicine physicians. The number of focal lesions, maximum standardized uptake value (SUVmax), presence of extramedullary disease, and diffuse bone marrow involvement were recorded. The metabolic risk classification used in the present study was adapted from the high-risk PET/CT features described by Terao et al.[7], who defined high-risk findings as the presence of more than three focal lesions, SUVmax >4.2, or extramedullary disease. For the present analysis, an SUVmax cutoff of >4 was selected as a pragmatic approximation of the >3.9 prognostic threshold reported by Bartel et al.[9] In addition, diffuse bone marrow involvement was incorporated into the composite classification based on the findings of Li et al,[8] who demonstrated that diffuse or mixed bone marrow FDG uptake patterns were independently associated with inferior progression-free and OS. Accordingly, patients were classified as having metabolically high-risk disease if at least one of the following features was present: more than three focal lesions, SUVmax >4, extramedullary disease, or diffuse bone marrow involvement. Patients without any of these findings were classified as having metabolically low-risk disease. This study-specific composite classification was used for exploratory risk stratification and was not intended to represent an established or externally validated clinical risk score.

The primary endpoint was to evaluate the association of baseline PET/CT findings and FISH-defined cytogenetic risk with early treatment response, including VGPR after the second cycle and ≥VGPR after the fourth cycle. Secondary endpoints were disease progression, PFS, and OS. PFS was defined as the time from diagnosis to disease progression or death from any cause, whichever occurred first. Patients alive and progression-free at last follow-up were censored at the date of last examination. OS was defined as the time from diagnosis to death from any cause.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). A two-sided p value of <0.05 was considered statistically

significant. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Descriptive statistics are presented as mean±standard deviation or median (range), as appropriate. Categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables were performed using the Pearson χ^2 test or Fisher's exact test, as appropriate. Survival outcomes were estimated using the Kaplan–Meier method and compared using the log-rank test. Variables with a p value <0.25 in the univariable analysis, together with clinically relevant variables, were entered into the multivariable Cox proportional hazards regression model using the enter method. Hazard ratios (HRs) with 95% confidence intervals, regression coefficients (B), standard errors (SE), and corresponding p values are reported.

RESULTS

A total of 70 patients with newly diagnosed MM were included in the study. The mean age was 65.0±9.2 years, and 36 (51.4%) patients were female. IgG was the most common myeloma subtype (44.3%), followed by free light chain (27.1%) and IgA myeloma (25.7%). According to the ISS, 20.0% of patients had stage I disease, 42.9% had stage II disease, and 37.1% had stage III disease. Based on the R-ISS, most patients (60.0%) were classified as stage II, whereas 27.1% had stage III disease.

Elevated serum LDH levels were observed in 23 patients (32.9%), and 21 patients (30.0%) were classified as having high-risk cytogenetics based on FISH analysis. Baseline PET/CT demonstrated more than three focal lesions in 48 patients (68.6%) and an SUV max >4 in 44 patients (62.9%). Extramedullary disease was detected in 19 patients (27.1%), whereas diffuse bone marrow involvement was observed in 33 patients (47.1%). Overall, 57 patients (81.4%) were classified as having metabolically high-risk disease according to the predefined PET/CT criteria. Baseline clinical and disease characteristics are summarized in Table 1.

Most patients (61/70, 87.1%) received a initial regimen based on bortezomib, cyclophosphamide, and dexamethasone (VCD), whereas the remaining initial treatment regimens were heterogeneous and represented by small patient numbers. Subsequent regimen modifications were frequently response-adapted following assessment after the second treatment cycle.

Treatment responses and clinical outcomes are presented in Table 2. After the second cycle of induction therapy, 30 patients (42.9%) achieved a VGPR, 37 (52.9%) achieved a partial response (PR), and only three patients had stable disease (SD) or progressive disease (PD). Following the fourth treatment cycle, the VGPR rate increased to 57.1%, while PR and PD were observed in 37.1% and 5.7% of patients, respectively. Overall, 40 patients (57.1%) achieved an early deep response (≥VGPR) after the fourth cycle.

During follow-up, 39 patients (55.7%) underwent ASCT. Disease progression occurred in 10 patients (14.3%), and six patients (8.6%) died; three deaths occurred after progression and three without documented prior progression. Thus, 13 PFS events (18.6%) were observed. At last follow-up, 64 patients (91.4%) were alive and 57 (81.4%) were alive and progression-free.

Table 1. Baseline clinical and disease characteristics of the patients

Parameter	n	%
Myeloma subtype		
IgG kappa	18	25.7
IgG lambda	13	18.6
IgA kappa	9	12.9
IgA lambda	9	12.9
IgM lambda	1	1.4
Free kappa	14	20.0
Free lambda	5	7.1
Non-secretory	1	1.4
ISS Stage		
Stage I	14	20.0
Stage II	30	42.9
Stage III	26	37.1
R-ISS Stage		
Stage I	9	12.9
Stage II	42	60.0
Stage III	19	27.1
Serum LDH		
Normal	47	67.1
Elevated	23	32.9
FISH-defined cytogenetic risk		
Standard	49	70.0
High	21	30.0
>3 focal lesions on baseline PET/CT		
Yes	48	68.6
No	22	31.4
SUVmax >4 on baseline PET/CT		
Yes	44	62.9
No	26	37.1
Extramedullary disease		
Present	19	27.1
Absent	51	72.9
Bone marrow involvement on PET/CT		
Present	33	47.1
Absent	37	52.9
Metabolically high-risk disease		
Yes	57	81.4
No	13	18.6

IgG: Immunoglobulin G, ISS: International Staging System, R-ISS: Revised International Staging System, LDH: Lactate dehydrogenase, FISH: Fluorescence in situ hybridization, SUVmax: Maximum standardized uptake value, IgA: Immunoglobulin A, IgM: Immunoglobulin M, PET/CT: Positron emission tomography/computed tomography

The median follow-up duration was 15.3 months (range, 3.6–29.1 months). Median PFS and OS were not reached during the study period. The estimated 1-year PFS and OS rates were 86% and 92%, respectively (Figure).

PFS and OS were compared according to gender, myeloma subtype, PET/CT findings, serum LDH level, FISH-defined cytogenetic risk, and depth of response after the fourth treatment cycle. Kaplan–Meier analysis demonstrated significantly longer PFS in female patients than in male patients (p=0.001). No significant differences in PFS were observed for the remaining variables, including ≥VGPR after the fourth cycle (p=0.116).

Table 2. Treatment response and clinical outcomes

Parameter	n	%
Response after the second cycle		
VGPR	30	42.9
PR	37	52.9
SD	2	2.9
PD	1	1.4
Response after the fourth cycle		
VGPR	40	57.1
PR	26	37.1
PD	4	5.7
≥VGPR after the fourth cycle		
Yes	40	57.1
No	30	42.9
Autologous stem cell transplantation (ASCT)		
Yes	39	55.7
No	31	44.3
Disease progression*		
Present	10	14.3
Absent	60	85.7
Vital status		
Alive	64	91.4
Dead	6	8.6

ASCT: Autologous stem cell transplantation, PD: Progressive disease, PFS: Progression-free survival, PR: Partial response, SD: Stable disease, VGPR: Very good partial response.*Death without prior progression: 3 (4.3%), PFS events: 13 (18.6%)

None of the evaluated variables showed a statistically significant association with OS. Because all female patients and all patients with extramedullary disease remained alive throughout follow-up, comparative OS analyses could not be performed for these subgroups.

Univariable and multivariable Cox regression analyses were performed to identify factors associated with PFS and OS. In the univariable analysis, gender was the only variable significantly associated with PFS. Male patients had a significantly higher risk of disease progression or death than female patients (HR=14.7, 95% CI 1.9-113.4, p=0.010). However, only one PFS event occurred among 36 female patients, compared with 12 events among 34 male patients. Therefore, the hazard ratio had a wide confidence interval and should be interpreted cautiously. Achievement of ≥VGPR after the fourth cycle was not significantly associated with PFS (HR=0.42, 95% CI 0.14-1.28, p=0.127). FISH-defined cytogenetic risk, PET metabolic risk, SUV max, number of focal lesions, extramedullary disease, and bone marrow involvement on PET/CT were not significantly associated with PFS. No significant prognostic factor for OS was identified in the univariable analysis.

A multivariable Cox proportional hazards model including age, gender, myeloma subtype, FISH-defined cytogenetic risk, SUVmax, and achievement of ≥VGPR after the fourth cycle identified female gender as the only variable significantly associated with PFS (HR=0.067, 95% CI 0.008-0.569, p=0.013). However, only 13 PFS events (10 progressions and three deaths without prior progression) were available for the six covariates included in the model, corresponding to approximately 2.2 events per variable, and only one event occurred among female patients. Therefore, the model was at substantial risk of overfitting, and its hazard ratios, standard errors, and p values should be considered unstable and exploratory. Accordingly, p values approaching the conventional significance threshold were not interpreted as evidence of prognostic associations. The results of the multivariable Cox regression analysis are summarized in Table 3.

Table 3. Multivariable Cox regression analysis for progression-free survival

Variable	B	SE	Wald χ^2	HR	95% CI	p
Age	0.056	0.042	1.763	1.058	0.974–1.149	0.184
Gender (female vs. male)	-2.710	1.095	6.130	0.067	0.008–0.569	0.013
FISH-defined cytogenetic risk (high vs. standard)	1.193	0.664	3.231	3.298	0.898–12.111	0.072
Baseline SUVmax (>4 vs. ≤4)	0.544	0.725	0.564	1.723	0.416–7.131	0.453
≥VGPR after the fourth cycle (yes vs. no)	-0.874	0.641	1.861	0.417	0.119–1.465	0.173
Myeloma subtype (non-IgG vs. IgG)	1.193	0.698	2.921	3.296	0.839–12.943	0.087

HR: Hazard ratio, SE: Standard error, VGPR: Very good partial response, SUVmax: Maximum standardized uptake value

Treatment responses according to FISH-defined cytogenetic risk are presented in Table 4. Although patients with high-risk cytogenetics showed numerically higher VGPR rates after both the second cycle (52.4% vs. 38.8%, p=0.307) and the fourth cycle (66.7% vs. 53.1%, p=0.429), neither difference reached statistical significance. Likewise, the distribution

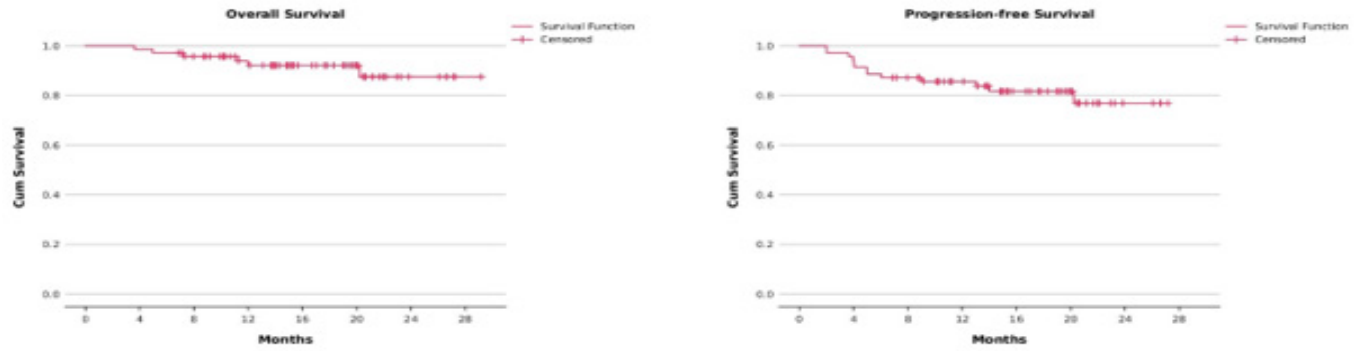


Figure. Kaplan–Meier curves for overall survival (left) and progression-free survival (right)

Table 4. Comparison of treatment response and disease progression according to FISH-defined cytogenetic risk

Parameter	Standard-risk cytogenetics (n=49, 70.0%)	High-risk cytogenetics (n=21, 30.0%)	OR (95% CI)	p
VGPR after the second cycle, n (%)	19 (38.8%)	11 (52.4%)	1.74 (0.62–4.87)	0.307
≥VGPR after the fourth cycle, n (%)	26 (53.1%)	14 (66.7%)	1.77 (0.61–5.14)	0.429
Response after the fourth cycle				
PD, n (%)	2 (4.1%)	2 (9.5%)	—	0.263
PR, n (%)	21 (42.9%)	5 (23.8%)	—	
VGPR, n (%)	26 (53.1%)	14 (66.7%)	—	
Disease progression during follow-up, n (%)	5 (10.2%)	5 (23.8%)	2.75 (0.70–10.77)	0.154

OR: Odds ratio, CI: Confidence interval, PD: Progressive disease, PR: Partial response, VGPR: Very good partial response

of treatment responses after the fourth cycle did not differ significantly between the two cytogenetic risk groups (p=0.263). Disease progression occurred more frequently in the high-risk cytogenetic group than in the standard-risk group (23.8% vs. 10.2%; OR=2.75, 95% CI: 0.70–10.77), although this difference was not statistically significant (p=0.154).

When patients were stratified according to PET/CT metabolic risk (Table 5), those with metabolically high-risk disease had significantly higher VGPR rates after the second treatment cycle (49.1% vs. 15.4%; OR=5.31, 95% CI: 1.08–26.14; p=0.032) and significantly higher ≥VGPR rates after the fourth cycle (64.9% vs. 23.1%; OR=6.17, 95% CI: 1.52–25.01; p=0.011) than patients with metabolically low-risk disease. In addition, the overall response distribution after the fourth cycle differed significantly between the two groups (p=0.005), indicating deeper treatment responses in patients with metabolically high-risk disease. However, the incidence of disease progression did not differ significantly between the metabolically low- and high-risk groups (7.7% vs. 15.8%; OR=2.25, 95% CI: 0.26–19.52; p=0.675).

Table 5. Comparison of treatment response and disease progression according to baseline PET/CT metabolic risk

Parameter	Metabolically low-risk disease (n=13, 18.6%)	Metabolically high-risk disease (n=57, 81.4%)	OR (95% CI)	p
VGPR after the second cycle, n (%)	2 (15.4%)	28 (49.1%)	5.31 (1.08–26.14)	0.032*
≥VGPR after the fourth cycle, n (%)	3 (23.1%)	37 (64.9%)	6.17 (1.52–25.01)	0.011*
Response after the fourth cycle				
VGPR, n (%)	3 (23.1%)	37 (64.9%)	—	
PR, n (%)	10 (76.9%)	16 (28.1%)	—	
PD, n (%)	0 (0%)	4 (7.0%)	—	0.005*
Disease progression during follow-up, n (%)	1 (7.7%)	9 (15.8%)	2.25 (0.26–19.52)	0.675

OR: Odds ratio, CI: Confidence interval, PET/CT: Positron emission tomography/computed tomography, PD: Progressive disease, PR: Partial response, VGPR: Very good partial response. The overall distribution of response categories after the fourth cycle was compared using the two-sided Fisher–Freeman–Halton exact test. *p<0.05

DISCUSSION

This study examined whether baseline metabolic imaging and cytogenetic risk assessment provide complementary information for predicting early therapeutic outcomes in newly diagnosed MM. Although metabolically high-risk patients achieved deeper responses during induction therapy, FISH-defined cytogenetic risk alone was not associated with early response or short-term progression. Female gender remained associated with longer PFS after multivariable adjustment, although this estimate was unstable, whereas ≥VGPR was not significantly associated with PFS.

Baseline 18F-FDG PET/CT has become an important imaging modality for risk stratification in MM because it provides functional information beyond conventional morphologic assessment.[11] Previous studies have demonstrated that a high number of focal lesions, elevated SUVmax, diffuse bone marrow uptake, and extramedullary disease may be associated with inferior survival outcomes.[9,12] In contrast, metabolically high-risk patients in our cohort achieved deeper early responses. High FDG uptake may reflect a large population of viable, metabolically active plasma cells capable of rapid cytoreduction. Conversely, low FDG avidity does not necessarily indicate indolent disease, because low hexokinase-2 expression may result in low-avidity or false-negative PET/CT findings.[13] Metabolically and secretory-active plasma cells may also be more dependent on cellular proteostasis and therefore initially more susceptible to proteasome inhibitor-based treatment, although these pathways were not directly evaluated in our study.[14]

Moreover, rapid response may coexist with aggressive and clonally heterogeneous disease, allowing treatment-resistant subclones to persist despite substantial initial cytoreduction. Previous studies have similarly reported that high-risk patients may be more likely to achieve an early response and that rapid responders may have higher LDH levels and inferior long-term outcomes.[15-17] Therefore, the observed early response may reflect initial treatment sensitivity rather than favorable disease biology.

Despite the superior early response observed in the metabolically high-risk group, progression rates did not differ significantly between the two metabolic risk groups. This apparent dissociation raises the possibility that rapid initial cytoreduction may not translate into durable disease control. In addition, treatment was selected according to clinical judgment rather than assigned within a standardized prospective protocol and could be modified according to the interim response. Therefore, differences in initial treatment selection, regimen intensity, and subsequent response-adapted modifications may have contributed to the observed early response. Longer follow-up and prospective studies using standardized treatment approaches are required to clarify whether this association reflects disease biology, treatment-related factors, or both.

High-risk cytogenetic abnormalities identified by FISH are well-established adverse prognostic factors in MM and are incorporated into current risk stratification systems.[1,18,19] In the present study, patients with high-risk cytogenetics demonstrated numerically higher response rates and a higher frequency of disease progression; however, none of these differences reached statistical significance. The limited sample size and the relatively small number of PFS events are the most likely explanations for these findings. In addition, FISH analysis was performed on unselected bone marrow aspirate samples without CD138-positive plasma cell enrichment. This may have reduced the sensitivity for detecting cytogenetic abnormalities, particularly in samples with a low plasma cell proportion or hemodilution, and may have resulted in some high-risk patients being misclassified as having standard-risk cytogenetics. Such misclassification could have attenuated the observed associations between FISH-defined risk and clinical outcomes.

Female gender was associated with longer PFS in both univariable and multivariable analyses. However, previous studies have reported conflicting results regarding the prognostic effect of gender in MM.[20,21] In our cohort, only one PFS event occurred among female patients, compared with 12 among male patients, resulting in a wide confidence interval around the hazard ratio. Therefore, this estimate is statistically unstable and may overestimate the true association; it should be considered hypothesis-generating, must be interpreted cautiously, and requires confirmation in larger cohorts.

Achievement of a deep response after induction therapy has consistently been associated with improved survival in previous studies.[16,17,22] In our cohort, ≥VGPR after the fourth treatment cycle was not significantly associated with PFS (log-rank p=0.116; multivariable HR=0.42, 95% CI 0.12–1.47, p=0.173), although fewer PFS events occurred among these patients (5/40 vs. 8/30). The limited number of events likely precluded the detection of an association reported in larger studies, and this finding should not be interpreted as evidence for or against a prognostic effect of response depth.

Limitations

Several limitations should be considered when interpreting our findings. The retrospective single-center design and relatively small cohort limit the generalizability of the results. Restricting inclusion to patients with available baseline PET/CT and FISH results may have introduced selection bias. The small metabolically low-risk subgroup (n=13) also reduced the precision of response estimates. These factors may have contributed to the observed association between high metabolic risk and deeper early responses. More importantly, the median follow-up duration was only 15.3 months, with only 13 PFS events (10 progressions and three deaths without progression) and six deaths in total; consequently, median PFS and OS were not reached. The survival analyses, particularly the multivariable Cox regression model, were therefore substantially underpowered and should be considered exploratory. Specifically, the model included six covariates for 13 PFS events, yielding approximately 2.2 events per variable. This low event-to-variable ratio creates a substantial risk of overfitting and unstable effect estimates. Therefore, neither the absence of statistically significant associations nor p values close to 0.05 should be used to draw definitive prognostic conclusions regarding the evaluated PET/CT or cytogenetic variables. Treatment selection was based on clinical judgment, and treatment modifications after the second cycle were frequently guided by the interim response. Therefore, the recorded four-cycle treatment sequence represented a post-baseline, response-dependent variable rather than a uniform baseline covariate. In addition, the small and highly imbalanced treatment subgroups precluded reliable adjustment for treatment regimen in conventional multivariable models. Consequently, residual confounding related to treatment selection and regimen intensity cannot be excluded. In addition, performing FISH without CD138-enriched plasma cell sorting may have reduced the detection of cytogenetic abnormalities and resulted in misclassification of some patients as cytogenetically standard risk. MRD assessment was unavailable and could not be incorporated into the prognostic evaluation. Finally, the metabolic risk classification used in this study was a study-specific composite adapted from previously reported adverse PET/CT features and has not been externally validated. Findings based on this classification should therefore be interpreted as exploratory and require confirmation in independent cohorts.

Despite these limitations, the study also has several strengths. To our knowledge, few studies have simultaneously evaluated FISH-defined cytogenetic risk and a composite metabolic risk classification based on baseline PET/CT findings in relation to early treatment response. Furthermore, all patients underwent baseline PET/CT before treatment initiation, and treatment responses were evaluated using uniform criteria, providing a uniformly assessed real-world cohort.

Our findings suggest that metabolic information obtained from baseline PET/CT may complement conventional cytogenetic risk assessment during the initial treatment period. Although metabolically high-risk disease was associated with a higher likelihood of achieving a deep early response, neither PET/CT metabolic risk nor FISH-defined cytogenetic risk was significantly associated with short-term disease progression. Larger prospective studies with longer follow-up are needed to clarify the combined prognostic value of metabolic imaging and cytogenetic risk assessment in newly diagnosed MM.

CONCLUSION

Baseline PET/CT and FISH-defined cytogenetic risk may provide complementary information during the initial assessment of newly diagnosed MM. Metabolically high-risk disease was associated with deeper early treatment responses but was not significantly associated with short-term disease progression, whereas FISH-defined cytogenetic risk was not associated with early response or progression in this cohort. However, the short follow-up duration and limited numbers of progression and death events preclude definitive conclusions regarding PFS, OS or the independent prognostic value of these variables. Therefore, the survival findings should be considered preliminary and require validation in larger prospective studies with longer follow-up.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Ethics Committee of İzmir City Hospital (Date: 29.04.2026, Decision No: 2026/280).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: MKY; Design: MKY; Control: ZNÖ, OB; Resources: MKY, ÖA, FAY; Materials: MKY, ÖA, FAY; Data Collection and/or Processing: MKY, ÖA, FAY; Analysis and/or Interpretation: MKY; Literature Review: MKY; Writing the Article: MKY; Critical Review: MKY, ÖA, FAY, ZNÖ, OB.

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Letter to the Editor

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Acquired amegakaryocytic thrombocytopenia: a diagnostic pitfall in refractory thrombocytopenia

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Dear Editor,

Acquired amegakaryocytic thrombocytopenia (AAT) is a rare hematologic disorder characterized by severe isolated thrombocytopenia caused by a selective reduction or complete absence of bone marrow megakaryocytes while other hematopoietic lineages remain relatively preserved. Because its initial clinical presentation frequently overlaps with immune thrombocytopenia (ITP), delayed diagnosis and prolonged exposure to ineffective ITP-directed therapies are common in clinical practice. Early recognition is essential, as untreated AAT may progress to irreversible marrow failure or evolve into clonal hematologic disorders in refractory cases.[1]

A 21-year-old female presented with severe mucocutaneous bleeding and isolated thrombocytopenia. Initial peripheral blood smear confirmed marked thrombocytopenia without schistocytes or circulating blasts. Based on isolated thrombocytopenia, she was initially diagnosed with ITP and treated sequentially with corticosteroids, intravenous immunoglobulin, and eltrombopag over approximately two months. The patient had no previous exposure to immune checkpoint inhibitors, cytotoxic chemotherapy, or other known marrow-suppressive medications. Her treatment before the diagnosis of AAT consisted of corticosteroids, intravenous immunoglobulin, and eltrombopag, which were administered after the initial clinical diagnosis of ITP. However, no hematologic response was achieved, and the patient became entirely transfusion dependent for platelets and red blood cells. Given this refractory course, a bone marrow evaluation was performed. Bone marrow examination demonstrated a hypocellular marrow with marked megakaryocytic depletion and hypoplastic myeloid and erythroid compartments with preserved maturation. The myeloid-to-erythroid ratio was 64:4 (16:1), and blasts accounted for 2% of nucleated cells. No significant dysplasia was identified. Although the aspirate was limited for megakaryocyte assessment, the biopsy demonstrated marked megakaryocytic reduction, further supported by CD61/CD42b immunohistochemical staining. The marked and disproportionate depletion of megakaryocytes in the setting of severe thrombocytopenia argued against the initial diagnosis of ITP and supported AAT, further supported by CD61/CD42b immunohistochemical staining. Cytogenetics, FISH, and a comprehensive 141-gene myeloid NGS panel showed no clonal abnormalities. Comprehensive workup successfully excluded HIV, HBV, HCV, CMV, EBV, parvovirus B19, autoimmune disorders, thymoma, large granular lymphocytic leukemia, and PNH. The patient had no history of exposure to immune checkpoint inhibitors, cytotoxic chemotherapy, or other marrow-suppressive medications before the onset of thrombocytopenia. Thus, a drug-induced etiology was considered unlikely. Congenital etiologies were considered unlikely given the normal previous hematologic history and negative MPL mutation analysis.

The pathogenesis of AAT involves immune-mediated suppression of megakaryopoiesis and stem-cell dysfunction.[1] Distinguishing AAT from ITP is essential because management strategies differ substantially. Unlike ITP, AAT patients show limited responses to standard immunosuppressants or TPO receptor agonists. First-line cyclosporine or antithymocyte globulin yields variable responses, and many patients ultimately require allogeneic hematopoietic stem cell transplantation (HSCT).[2] HLA-matched siblings are traditionally preferred; however, recent evidence increasingly supports alternative strategies including haploidentical HSCT in selected amegakaryocytic settings.[3] Although the hypocellular marrow raised the differential diagnoses of hypoplastic myelodysplastic syndrome and early aplastic anemia, the absence of significant dysplasia, the low blast percentage (2%), the marked megakaryocytic depletion, and the absence of demonstrable clonal abnormalities favored AAT in the clinical context.

This case highlights the importance of timely recognition of severe, refractory AAT and the potential role of allogeneic HSCT as a definitive treatment in selected patients. Our

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patient remained profoundly thrombocytopenic, with severe refractory disease and no HLA-matched sibling donor. She underwent haploidentical allogeneic HSCT from her father on 28 April 2024. The available records did not contain sufficient information regarding the specific conditioning regimen and doses, neutrophil and platelet engraftment dates, or post-transplant donor chimerism; therefore, these parameters could not be reliably reported. Following transplantation, the patient achieved hematologic recovery and became transfusion independent. At the latest documented assessment, hemoglobin was 13.5 g/dl, platelet count was 175×10^3/μL, and white blood cell count was 7.61×10^3/μL. No graft-versus-host disease or other major transplant-related complication was documented. Persistent isolated thrombocytopenia unresponsive to standard ITP therapies should prompt timely bone marrow evaluation to avoid prolonged ineffective treatment and facilitate prompt access to definitive therapies including allogeneic HSCT.[4]

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient for the publication of this correspondence and any related clinical details.

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The author declares no conflicts of interest.

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Author Contributions

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