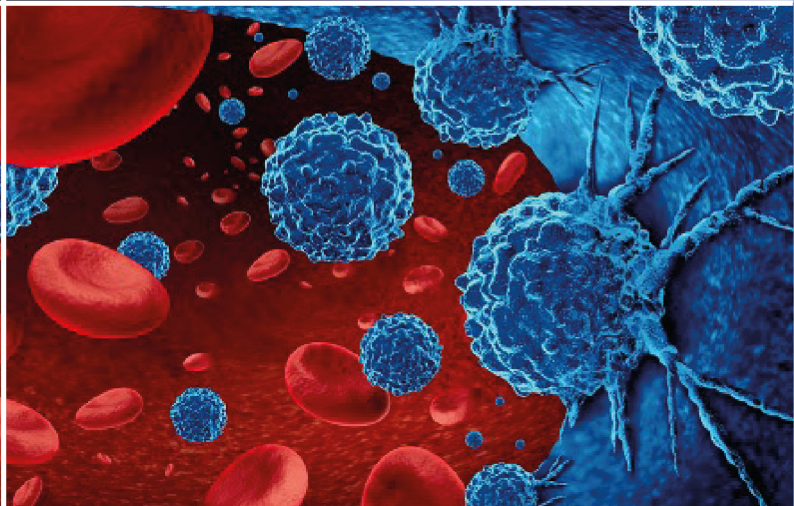
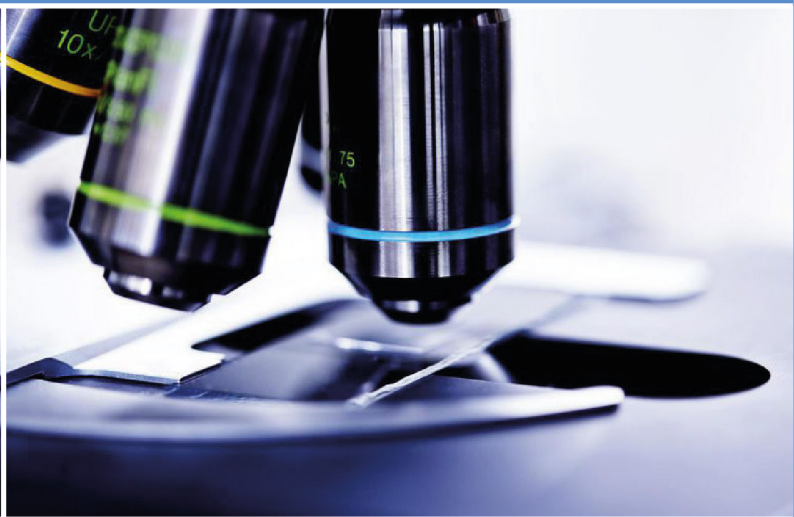
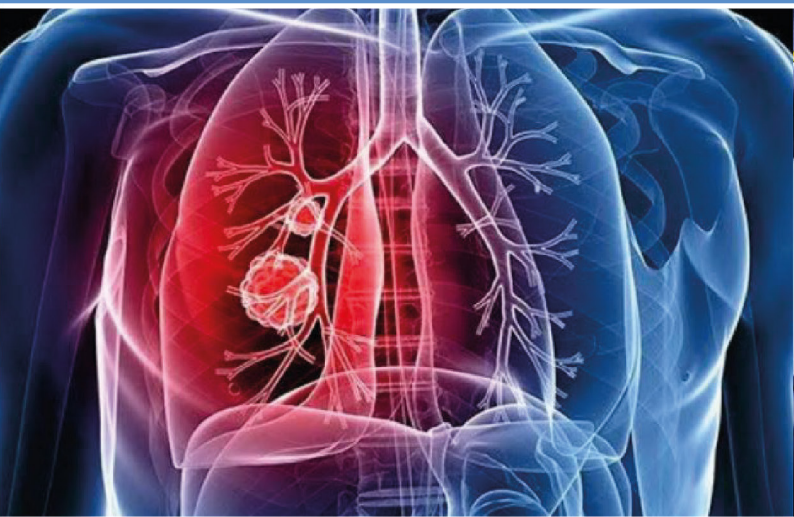


JCHOR

Journal of Current Hematology & Oncology Research



Volume: 4

Issue: 2

Year: 2026

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Retrospective analysis of glial tumors in light of the 2016 WHO classification of central nervous system tumours diagnosed at a single center between 2005 and 2016

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Cite this article: Bakoğlu Malinowski N, Çakır E, Saygın İ. Retrospective analysis of glial tumors in light of the 2016 WHO classification of central nervous system tumours diagnosed at a single center between 2005 and 2016. *J Curr Hematol Oncol Res.* 2026;4(2):31-39. doi:10.51271/JCHOR-0079

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Received: 11/02/2026

Accepted: 12/04/2026

Published: 18/05/2026

ABSTRACT

Aims: The 2016 WHO Classification of Tumors of the Central Nervous System introduced a paradigm shift by integrating molecular features with traditional histomorphology. This study aims to retrospectively re-evaluate glial tumor cases from a major tertiary center in light of these evolving classification criteria and provide a baseline for future molecular research.

Methods: A retrospective analysis was conducted on 395 glial tumor cases diagnosed at the Karadeniz Technical University Faculty of Medicine, Department of Pathology, between 2005 and 2016. The cases were re-grouped according to the 2016 WHO criteria. Due to the lack of molecular data available during the archival period, cases were categorized under the “not otherwise specified” (NOS) group to establish a comprehensive database.

Results: Among the 395 cases analyzed, glioblastoma was identified as the most frequent histological subtype (n=235). A male predominance was observed (56.5%), with mean and median ages of 48.21 and 50 years, respectively. The most common anatomical location was the frontal lobe, and histological grade IV was the most prevalent grade. Statistical analyses revealed a highly significant association between advancing age and higher tumor grade ($\chi^2=68.45$, $p<.001$), while gender distribution remained homogeneous across major histological groups ($p=0.042$). These demographic and distribution data were consistent with global literature.

Conclusion: The findings align with international demographic trends while highlighting the practical challenges of transitioning to molecular-based classifications. While the subsequent 2021 WHO Classification further emphasizes IDH status, “histologically defined” or “NOS” designations remain crucial for regions where molecular testing infrastructure is limited. This study provides a robust archival baseline that facilitates future molecular studies and serves as a reference for glial tumor characterization in resource-constrained settings.

Keywords: Central nervous system, 2016 WHO classification, glial tumors

INTRODUCTION

Glial tumors are the most common type of brain tumors. Twenty percent (20%) of glial tumors are low-grade glial tumors.¹ The most frequently seen tumour is glioblastoma.² For nearly a century, the classification of brain tumors was determined based on their histomorphological characteristics, which rely on assumed cellular origins and microscopic similarities. These similarities were characterized by the light microscopic appearance of Hematoxylin & Eosin (H&E)-stained sections, immunohistochemical expressions, and electron microscopic appearances. The 2007 WHO (World Health Organization) classification grouped glial tumors as oligodendroglial or astrocytic according to their phenotype, regardless of whether they were clinically similar or distinct.³ Genetic studies conducted in the past two decades have contributed to a better understanding and classification of these tumors.⁴ The importance of the genetic

profile is increasing because some genetic alterations (e.g., isocitrate dehydrogenase (IDH) mutation in diffuse gliomas) have been found to have significant prognostic meaning.^{5,6} The 2016 WHO classification categorized brain tumors not only by light microscopy findings but also by incorporating molecular studies. According to the WHO 2016 classification criteria for central nervous system (CNS) tumors, gliomas are grouped as diffuse astrocytic and oligodendroglial tumors, other astrocytic tumors, ependymal tumors, and other gliomas. Diffuse astrocytic and oligodendroglial tumors were subclassified as diffuse astrocytoma, anaplastic astrocytoma, glioblastoma, diffuse midline glioma, oligodendrogloma, anaplastic oligodendrogloma, oligoastrocytoma, and anaplastic oligoastrocytoma. Diffuse astrocytomas were divided into three categories: IDH-mutant, IDH-wildtype, and not otherwise specified (NOS), while ‘gemistocytic

astrocytoma' was specified as a subtype of diffuse astrocytoma. Similarly, anaplastic astrocytoma and glioblastoma were also classified according to IDH mutation. Giant cell glioblastoma, gliosarcoma, and 'epithelioid glioblastoma,' which was absent in the 2007 WHO classification, were defined as subtypes of glioblastoma. Diffuse midline glioma was specified as H3K27M-mutant. Oligodendroglioma and anaplastic oligodendroglioma were divided into two categories: IDH-mutant and 1p/19q co-deleted, and NOS. Oligoastrocytoma and anaplastic oligoastrocytoma were defined as NOS. Other astrocytic tumors were divided into four subgroups: pilocytic astrocytoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, and anaplastic pleomorphic xanthoastrocytoma, which was absent in the 2007 WHO classification. Ependymal tumors were divided into five groups: subependymoma, myxopapillary ependymoma, ependymoma, ependymoma RELA fusion-positive, and anaplastic ependymoma. Ependymoma, in turn, was defined in three subgroups as papillary, clear cell, and tancytic ependymoma, and the 'cellular type' from the WHO 2007 classification was removed.⁷ However, the 2021 classification incorporates additional information derived from genomic studies^{8,9} various changes have been made regarding the diagnostic principles and nomenclature of diffuse gliomas, which have led to important implications for clinical practice and the design and interpretation of clinical research.¹⁰ According to the 2021 classification, the main group "diffuse astrocytic and oligodendroglial tumors" defined in 2016 has been divided into "adult-type and pediatric-type diffuse astrocytomas" for cases above and below 18 years of age. The "other astrocytic" and "other gliomas" groups have been moved into the "circumscribed astrocytic tumors" group. Within the diffuse astrocytic and oligodendroglial tumors group, diffuse midline glioma has been separated into low-grade and high-grade, and "pediatric diffuse gliomas" have been included in the high-grade classification, with the term H3K27M 'mutant' being replaced by 'altered.' Furthermore, six new molecular types have been defined and added to the pediatric diffuse glioma groups.¹¹

According to GLOBOCAN data CNS tumor cases in Türkiye increased from 2,087 in 2012 to 3,907 in 2020.¹²⁻¹⁴ CBTRUS (Central Brain Tumor Registry of The United States) data indicate that 32.8% of CNS tumors are malignant with a higher prevalence in males (55%) while benign tumors are more frequent in females (64%).² Between 2016-2020 the average annual age-adjusted incidence rate (AAAIR) was 25.34 per 100,000, consistently appearing higher in females than males.¹⁴ Anatomically, the meninges represent the most common tumor site, increasing from 36.4% in 2014 to 42% in 2022, followed by the frontal and temporal lobes. Histologically, meningioma remains the most frequent diagnosis (41.8% in 2022), followed by pituitary tumors and glioblastoma. Glioblastoma is the most prevalent malignant histology, accounting for 51.5% of cases in 2022, while gliomas overall comprise approximately 22.9% to 27% of all CNS tumors.^{15,16} The development of CNS tumors is influenced by various environmental and occupational factors, with ionizing radiation and X-ray therapy identified as the most definitive risk factors for meningioma, sarcoma, and astrocytoma.¹⁷⁻¹⁹ Histological grading, which determines the biological behavior of a neoplasm, plays a key role in specific chemotherapy protocols and adjuvant radiation

treatments. Grade 1 and 2 tumors (low grade) exhibit lower potential for malignant progression into high grade (grade 3 and +) tumors.^{20,21}

Although the fifth edition of the WHO Classification of Tumours of the CNS (2021) introduced significant changes—including the transition to Arabic numerals for grading and the integration of molecular markers such as IDH-mutation status and CDKN2A/B homozygous deletion for diagnosis—these updates are still being integrated into longitudinal statistical reporting. The molecular landscape of gliomas is defined by specific genetic alterations that serve as critical diagnostic, prognostic, and predictive markers^{14,23,24} (Figure 1).^{25,26} Notably, 1p/19q codeletion is established as a predictive marker for response to procarbazine, CCNU, and vincristine (PCV) chemotherapy in oligodendroglial tumors.²⁷⁻²⁹ While increased EGFR activity is frequently observed in advanced-stage tumors and aids in characterization, other biomarkers such as MGMT promoter methylation status remain vital for predicting treatment response in IDH-wildtype glioblastoma.^{30,31} Under the current diagnostic framework, IDH-wildtype diffuse gliomas (grades II-III) require investigation of TERT promoter mutations, EGFR amplification, and chromosome +7/-10 gain/loss to confirm molecular status. Furthermore, specific clinical contexts necessitate targeted testing: H3 K27 alterations for midline tumors, H3 G34 for pediatric and young adult IDH-wildtype cases, and MYB/MYBL1 or FGFR1 for pediatric low-grade patterns.³² Modern classification now groups diffuse gliomas based on growth patterns integrated with driver mutations in IDH1 and IDH2.⁵ In practice, while many markers like ATRX and TP53 can be assessed via immunohistochemistry, confirming 1p/19q codeletion status typically requires specialized molecular techniques such as fluorescence in situ hybridization (FISH).³³ According to the 2016 WHO classification, diagnosis was designated as NOS if molecular studies could not be performed or did not yield meaningful results. In the 2021 classification, the NOS designation has been removed, and all glial tumors are classified according to the molecular results; however, the histologically-based classification remains valid for countries lacking molecular laboratories or those with low income (Figure 2).⁵ Under the 2021 update, the classification of adult-type diffuse gliomas is primarily dependent on IDH1/2 mutation and 1p/19q codeletion status, resulting in three distinct groups: IDH-mutant and 1p/19q-codeleted oligodendroglioma, IDH-mutant astrocytoma (1p/19q non-codeleted), and IDH-wildtype glioblastoma. This revision strictly separates IDH-mutant from IDH-wildtype disease—a necessity given the substantial survival discrepancy between the two, even among tumors sharing the same histopathological feature.³⁴ We aimed to retrospectively evaluate glial tumor cases diagnosed at Karadeniz Technical University Faculty of Medicine Hospital between 2005 and 2016 according to the 2016 WHO classification, intending to create a resource to contribute to future molecular studies.

METHODS

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 28.11.2016, Decision No: 2016169). The authors

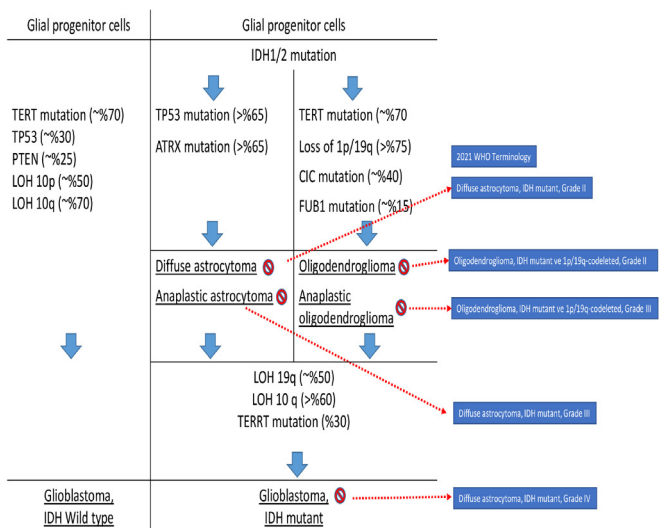


Figure 1. Genetic parameters of glial cells and the IDH1/2 molecular pathway, IDH status in glioblastomas, and terminological shifts between 2016 and 2021. The left panel shows the genetic pathway based on the primary vs. secondary glioblastoma distinction (WHO 2016); the right panel (highlighted in blue) illustrates how this terminology evolved in the WHO 2021 classification. IDH: Isocitrate dehydrogenase

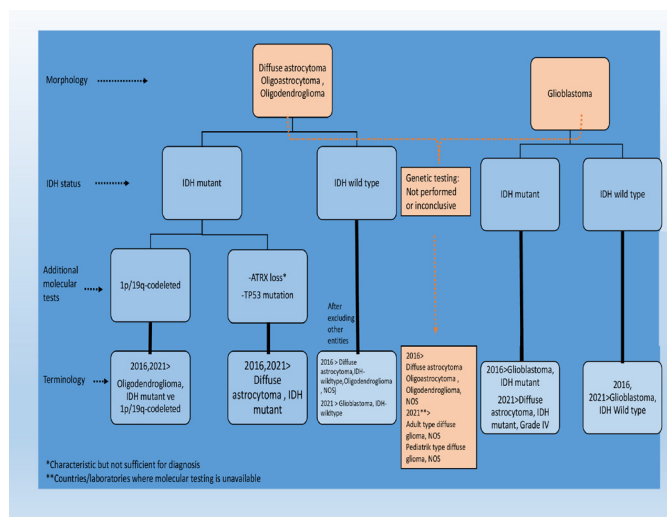


Figure 2. Comparison of genetic parameters used in clinical practice and terminology according to the 2016 and 2021 WHO classifications. While the 2016 WHO classification follows a histology-first followed by IDH mutation sequence, the 2021 WHO adopts IDH mutation as the primary step. A key change, besides the separation of adult and pediatric glial tumors, is that high-grade glial tumors with IDH mutations are now defined as "Astrocytoma, IDH-mutant, grade 4" instead of "glioblastoma, grade 4." IDH: Isocitrate dehydrogenase

declared that this study has received no financial support. Our study consisted of glial tumors diagnosed at the Pathology Laboratory of Karadeniz Technical University Faculty of Medicine between 2005 and 2016. A total of 428 glial tumor cases were identified in our laboratory. Twenty-nine cases were excluded from the study because their histological grades were not assigned. The cases included in this study were diagnosed by experienced senior neuropathologists at a tertiary referral center, following the diagnostic gold standard of the respective period. To ensure the integrity of the archival data and to avoid potential inter-observer variability, the original pathological diagnoses and histological grades were strictly maintained. This approach preserves the real-world diagnostic performance of the center during the 11-year study period.

Statistical Analysis

The data analyses were performed on a total of 395 glial tumor cases. Parameters that could be compared, such as demographic findings (age, sex, and location), were determined based on the pathological diagnosis. Statistical analyses were performed by grouping the cases according to the 2016 WHO classification. The cases were evaluated across four main histological groups: 1) Diffuse astrocytic and oligodendroglial tumors, 2) Other astrocytic tumors, 3) Ependymal tumors, and 4) Other gliomas. The main groups were further divided into subgroups. In our study, all subgroups were compared with demographic characteristics. Statistical analyses were conducted with support from the Department of Public Health at Karadeniz Technical University Faculty of Medicine using SPSS 23.00. The 'sensitivity-specificity' test was applied for the use of qualitative data. Count data were expressed as percentages. While qualitative data were specified as numbers and percentages, measurement data were used by providing the median and mean values. Statistical analyses were performed using SPSS software (SPSS v23). Continuous variables such as age were expressed as mean, median, and range. Categorical variables (sex, location, subtype) were presented as frequencies and percentages. To evaluate the relationship between histological subtypes and clinical parameters (age groups, sex, and anatomical localization), Pearson Chi-square (χ^2) tests or Fisher's exact tests were utilized where appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic data for all glial tumors (histological subtypes, case numbers and percentages, case count per histological subtype, minimum, maximum age, mean, and median age values) are summarized in **Table 1**.

Distribution of Glial Tumors According to Their Histological Subtypes

The study cohort comprised a total of 395 glial tumor cases, which were categorized into four primary groups according to the 2016 WHO classification system. The most prevalent category was diffuse astrocytic and oligodendroglial tumors, accounting for 319 cases (80.8%), followed by ependymal tumors (49 cases; 12.4%) and other astrocytic tumors (27 cases; 6.8%); notably, no cases of "other gliomas" (group 4) were identified within the archive. Within the dominant first group, glioblastoma was the most frequent histological subtype (235 cases; 73.7%), followed by diffuse astrocytoma (13.8%), oligodendroglioma (4.7%), anaplastic astrocytoma (4.1%), and anaplastic oligodendroglioma (3.8%). Regarding group 2 ("other astrocytomas"), pilocytic astrocytoma constituted nearly the entire subset (26 of 27 cases), while group 3 (ependymal tumors) was primarily represented by ependymoma (67.3%), with smaller distributions of myxopapillary ependymoma (22.4%), anaplastic ependymoma (8.2%), and subependymoma (2%). Aggregated data across the entire 395-case series identifies glioblastoma as the overall most common diagnosis (59.5%), followed in descending order of frequency by diffuse astrocytoma (11.1%), all ependymoma (8.4%), and pilocytic astrocytoma (6.6%), with all remaining subtypes individually accounting for less than 4% of the total archive.

Table 1. Histological subtypes of all glial tumors: case numbers and percentages, case distribution across subtypes, minimum and maximum age ranges, and mean and median age values

Glial tumors	Percentage	Female	Male	Minimum age	Maximum age	Mean age	Medium age
Diffuse astrocytic and oligodendroglial tumors	80.80%	131	188	1	82	53.06	56
Diffuse astrocytoma	11.10%	20	24	1	81	42.57	41
Anaplastic astrocytoma	3.30%	3	10	7	76	46.31	37
Glioblastoma	59.50%	95	140	1	82	56.83	59
Oligodendroglioma	3.80%	7	8	13	71	38.27	37
Anaplastic oligodendroglioma	3%	6	6	30	57	43.58	45
Other astrocytic tumors	6.80%	15	12	2	41	14.74	14
Pilocytic astrocytoma	6.60%	15	11	2	41	14.69	13.6
Pleomorphic xanthoastrocytoma	0.30%	0	1	16	16	16	16
Ependymal tumors	12.40%	26	23	1	75	35.1	35
Myxopapillary ependymoma	2.80%	5	6	12	65	37.18	35
Ependymoma	8.40%	19	14	1	75	38.18	38
Anaplastic ependymoma	1%	1	3	2	17	9	8.5
Subependymoma	0.30%	1	0	15	15	15	15
Total	100%	172	223	1	82	48.21	50

Distribution of Glial Tumors by Sex

The study cohort comprised 395 glial tumor cases, exhibiting a male predominance of 56.5% (n=223) compared to 43.5% females (n=172). Across both gender cohorts, glioblastoma was identified as the most prevalent histological entity, representing 55.2% of female and 62.8% of male cases. In both groups, diffuse astrocytoma followed as the second most common subtype, occurring in 11.6% of females and 10.8% of males. Subsequent distributions for both cohorts included ependymoma, pilocytic astrocytoma, and various anaplastic variants, as detailed in **Table 1**. Analysis of sex-based distribution within the WHO 2016 classification groups revealed distinct patterns. Group 1 (diffuse astrocytic and oligodendroglial tumors; n=319) showed a significant male bias at 58.9%. Within this category, glioblastoma (n=235) and diffuse astrocytoma (n=44) both demonstrated a higher frequency in males (59.6% and 54.5%, respectively), while anaplastic oligodendrogliomas displayed an equal gender distribution (50% each). Conversely, a slight female predilection was observed in group 2 (other astrocytomas, 55.6%) and group 3 (ependymal tumors, 53.1%). Specifically, females constituted the majority of cases for pilocytic astrocytoma (57.7%) and ependymoma (57.6%). In contrast, rarer entities such as anaplastic ependymoma and pleomorphic xanthoastrocytoma were predominantly or exclusively identified in male patients (**Table 1**).

Distribution of Glial Tumors by Age

The study population (n=395) exhibited an age range of 1 to 82 years, with a mean age of 48.21 years and a median of 50 years. Analysis by WHO classification groups revealed distinct chronological profiles: the “diffuse astrocytic and oligodendroglial tumors” group showed the highest mean age (53.06 years), whereas “other astrocytomas” (primarily pilocytic) and “ependymal tumors” occurred in significantly younger populations, with mean ages of 14.74 and 35.10 years, respectively (**Table 1**). Age-specific histological trends were highly pronounced when stratified by the 50-year threshold. In the under-50 cohort (n=185), glioblastoma was the most frequent diagnosis (32.4%), followed by diffuse astrocytoma

(15.7%) and ependymoma (14.6%). In sharp contrast, the over-50 cohort (n=210) was heavily dominated by glioblastoma, which accounted for 83.3% of all cases in this demographic. Further stratification into three age tiers—pediatric/adolescent (<20), young adult (20–39), and mature adult (>39)—underscored a clear pathological shift: Under 20 years (10.6%): Pilocytic astrocytoma was the predominant entity (47.6%), while glioblastoma was rare (16.7%). 20–39 years (18.5%): The diagnostic landscape was more heterogeneous, led by diffuse astrocytoma (24.7%) and ependymoma (20.5%). Over 39 years (70.9%): Glioblastoma became the definitive majority (76.8%), followed by diffuse astrocytoma (8.2%). Notably, anaplastic ependymomas were confined to a pediatric/adolescent window (mean age: 9 years), whereas glioblastomas reached their peak incidence in the sixth decade of life (mean age: 56.83). These findings highlight a strong correlation between advancing age and the increased prevalence of high-grade glial malignancies (**Table 1**).

Distribution of Glial Tumors According to Their Locations

Among the 395 glial tumor cases analyzed, the frontal lobe was the most prevalent site of localization, accounting for 28.4% of cases (n=112), followed by the parietal (26.3%) and temporal (23.3%) lobes. Less frequent sites included the spinal cord (10.1%), the posterior fossa (7.6%), and the occipital lobe (2.3%), with minimal involvement observed in the ventricles, basal ganglia, and corpus callosum. Histological sub-analysis revealed distinct anatomical preferences: diffuse astrocytomas (n=44) and oligodendrogliomas (n=15) predominantly favored the frontal lobe at 38.6% and 86.7%, respectively, while anaplastic astrocytomas (n=13) were most common in the temporal lobe (38.5%). Glioblastomas (n=235) demonstrated a relatively even distribution across the temporal (32.3%), parietal (31.9%), and frontal (29.8%) lobes. Notably, pilocytic astrocytomas (n=26) showed a strong predilection for the posterior fossa (73.1%), whereas ependymal tumors were largely concentrated in the spinal cord, including 100% of myxopapillary ependymomas (n=11) and 69.7% of standard ependymomas (n=33). Conversely, anaplastic ependymomas were primarily localized to the

posterior fossa (75%). Rare instances, such as pleomorphic xanthoastrocytoma and subependymoma, were isolated to the parietal lobe and lateral ventricle, respectively.

Distribution of Glial Tumors According to Their Histological Grades

In 395 glial tumors, 235 cases (59.5%) were found to be grade 4. The number of grade 2 cases is 91 (23%), grade 1 cases is 39 (9.9%), and grade 3 cases is 30 (7.6%). The majority of the 44 diffuse astrocytoma cases are grade 2, with 42 cases (95%), while the remaining 2 cases (4.5%) are grade 3.

Comparative Analysis of Histological Subtypes, Age, Sex, and Localization

The clinico-anatomical distribution and histological grading of the 395 glial tumor cases are summarized in **Table 2**. Statistical analysis revealed a highly significant correlation between histological subtype and anatomical localization (Fisher’s exact test, $p < 0.001$). The frontal lobe was the most frequent site overall (28.4%); however, distinct predilections were observed for specific subtypes: 86.7% of oligodendrogliomas were localized to the frontal lobe, while 73.1% of pilocytic astrocytomas were situated in the posterior fossa. Notably, all myxopapillary ependymomas (100%) and a vast majority of standard ependymomas (69.7%) were identified within the spinal cord. Regarding demographics, a significant association was found between patient age and tumor type (χ^2 test, $p < 0.001$). While the cohort’s median age was 50 years, glioblastoma (the most prevalent subtype at 59.5%) showed a marked concentration in the older population, representing 83.3% of all cases in patients aged ≥ 50 . Conversely, pilocytic astrocytoma was the dominant diagnosis in the pediatric and adolescent group (under 20 years), accounting for 47.6% of cases in that bracket. Gender distribution also showed a statistically significant male predominance overall (56.5%, $p = 0.042$), which was most pronounced in the anaplastic astrocytoma subgroup (76.9% male). Finally, histological grading reflected a high prevalence of aggressive malignancies, with grade IV (glioblastoma) constituting 59.5% of the total cohort, followed by grade II tumors (23%).

DISCUSSION

Histologic Subtypes

Glioblastoma remains the most prevalent primary malignant brain tumor globally.³⁵⁻³⁷ In our cohort, glioblastoma accounted for 59.5% of cases, aligning with the 2022 CBTRUS report, which identifies diffuse astrocytic and oligodendroglial tumors as the most frequent CNS category (18.8%), with glioblastoma maintaining the highest incidence (14.2%).³⁸ Following glioblastoma, diffuse astrocytomas constituted our second largest group (11.1%), a distribution consistent with most Western literature but contrasting with data from the Brain Tumor Registry of Japan (BTJ), where anaplastic astrocytomas occurred more frequently.³⁹ While recent literature emphasizes the prognostic weight of molecular markers—noting that IDH-wildtype cases comprise the vast majority (78.5%) of glioblastomas³⁹—our cases are classified as NOS due to a lack of molecular profiling. Despite this, the transition from the 2016 to the 2021 WHO Classification does not significantly alter our primary categorical findings. The 319 diffuse tumors in our study would largely redistribute into the 2021 “adult-type diffuse gliomas” category (306 cases), while our “other astrocytic tumors” would align with “circumscribed astrocytic gliomas.” Critically, the demographic trends observed in our cohort—including age, sex, and localization—remain diagnostically valid and clinically relevant across both classification frameworks. A recent study at Prof. Dr. Cemil Taşcıoğlu City Hospital in Türkiye (2023) confirm that high-grade gliomas (HGG) dominate clinical cohorts in Turkish tertiary centers.⁴⁰ In a Turkish study published in the Turkish Neurosurgery (2021), glioblastoma was consistently the primary diagnosis, mirroring our 59.5% rate.⁴¹

Sex

The 2016 CBTRUS report indicates a female predominance (57.9%) in the overall incidence of brain tumors. In contrast, malignant tumors are more common among males, who represent 55.2% of such cases. Furthermore, all glial tumor types—excluding pilocytic astrocytomas—demonstrate a higher frequency in the male population.² According to

Table 2. Clinicopathological characteristics and anatomical distribution of glial tumors in relation to histological grading and patient demographics (n=395)

Histological subtype	n (%)	Mean age	Gender (F/M)	Primary localization (%)	WHO grade
Glioblastoma	235 (59.5%)	56.8	95 / 140	Temporal (32.3%)	IV
Diffuse astrocytoma	44 (11.1%)	42.6	20 / 24	Frontal (38.6%)	II
Ependymoma	33 (8.4%)	38.2	19 / 14	Spinal cord (69.7%)	II
Pilocytic astrocytoma	26 (6.6%)	14.7	15 / 11	Post. fossa (73.1%)	I
Oligodendroglioma	15 (3.8%)	38.3	7 / 8	Frontal (86.7%)	II
Anaplastic astrocytoma	13 (3.3%)	46.3	3 / 10	Temporal (38.5%)	III
Anaplastic oligo	12 (3.0%)	43.6	6 / 6	Frontal/parietal (50%)	III
Myxopapillary epend	11 (2.8%)	37.2	5 / 6	Spinal cord (100%)	I
Anaplastic ependymoma	4 (1.0%)	9.0	1 / 3	Post. fossa (75%)	III
Others (PXA, subepend.)	2 (0.6%)	-	1 / 1	Various	I/II
Total/overall	395 (100%)	48.2	172 / 223	Frontal (28.4%)	-
Statistical analysis		$p < 0.001^*$	$p = 0.042$	$p < 0.001^*$	

F: Female, M: Male

2022 worldwide cancer statistics, primary malignant brain tumors exhibited a male disparity; of the 321,731 diagnosed cases, 173,699 were male and 148,032 were female.⁴² Males predominated in several categories, including diffuse astrocytic and oligodendroglial tumors (48% to 35%), other astrocytic tumors (3% to 2.9%), ependymal tumors (3.9% to 2.9%), and other gliomas (4.4% to 4.3%). Conversely, oligodendroglioma and oligoastrocytoma showed a female-to-male disparity favoring females. Similarly, a retrospective Japanese study of glial tumors reported a cohort of 149 females and 238 males, with a median age of 60 (range 3–88 years).⁴³ In alignment with existing literature, our findings showed a male predominance (56.5%) in glial tumors. Contrary to the 2015–2019 data, however, female predominance was observed in both pilocytic astrocytomas and ependymal tumors. Furthermore, Ohgaki et al.²⁴ reported glioblastoma incidence rates of 3.32 and 2.24 per 100,000 for males and females, respectively. In the United States, higher incidence rates have been reported, specifically 2.88 and 4.63 per 100,000 for females and males, respectively. CBTRUS reports from 2009–2013 identified a 1.57-fold higher incidence of glioblastoma in males compared to females, a figure that declined to 1.4 in the 2015–2019 period. Similarly, a study based in the UK documented a higher male-to-female ratio of 1.66.⁴⁴ The corresponding ratio in our study was 1.47, falling within the range reported in the literature. A Turkish study (Bilgin et al.,⁴⁰ 2021) reported a mean age of 56.4 for primary glioblastoma with a 56.9% male ratio. This almost perfectly matches our mean age (56.8) and male percentage (56.5%). Data from Erciyes University (2017) regarding childhood glial tumors in Turkiye shows a median age at diagnosis was 17 months, with pilocytic astrocytoma being the most common.⁴⁵ Our pediatric concentration in the 0–9 age group (45%) aligns with these national statistics.

Age

Age-stratified distribution and pediatric vs. adult disparities CNS neoplasms represent the most prevalent malignancy in the 0–14 age group, with incidence rates increasing significantly into adulthood.⁴⁶ Our cohort's demographic profile strongly correlates with these global trends, with 375 of 395 cases occurring in patients older than 10 years. While CBTRUS 2009–2013 data identifies a peak incidence in the ≥85 age group (84.52 per 100,000), our findings confirm that glial tumors remain predominantly a disease of the elderly, evidenced by the marked statistical divergence between pediatric and adult populations.^{2,12} The pediatric landscape: pilocytic astrocytoma in the pediatric population, pilocytic astrocytoma emerged as the predominant subtype. In our study, this was particularly evident in the 0–9 age range, where it accounted for 45% of glial tumors—a finding that mirrors the 2015–2019 CBTRUS data (incidence: 1.13).⁴⁷ Notably, this subtype was entirely absent in our cohort over 50 years of age. While the BTJ identifies diffuse astrocytoma as the most frequent subtype in patients under 20, our data showed pilocytic astrocytoma (47.6%) as the primary diagnosis, followed by glioblastoma (16.7%). This higher-than-expected frequency of glioblastoma in our younger patients represents a slight deviation from the BTJ findings but aligns with 2023 CBTRUS updates, which rank malignant ependymal tumors and glioblastomas as secondary frequent types in the 0–19 bracket.^{13,36} Adult and elderly populations: glioblastoma dominance for patients over 50, glioblastoma was

the overwhelmingly dominant subtype, representing 83.3% of cases. This aligns with the mean age of 62 years reported by Ohgaki et al.,²⁴ and the median age of 65 documented for IDH-wildtype astrocytomas. The age-dependent increase in glioblastoma incidence—rising from 5% in our 0–9 age group to 61.3% in those older than 10—confirms the progressive risk associated with advancing age identified in the BTJ and CBTRUS datasets.^{40,49} Our median age results showed a minimal discrepancy of only 1–2 years compared to international literature, reinforcing that our cohort serves as a representative model for the typical pediatric-to-adult distribution of glial neoplasms.

Location

Anatomical distribution analysis revealed that 80% of glial tumors in this cohort were localized within the cerebral lobes, with the frontal lobe (28.4%) being the most prevalent site, followed by an equal distribution between the parietal and temporal lobes (26.3% each). While these findings generally align with CBTRUS 2016–2020 data—which identifies the frontal and parietal regions as primary sites (16.6% and 7.4%, respectively)—our results demonstrate a distinct temporal lobe parity.^{13,50} Subtype-specific topography corroborated the strong frontal lobe affinity reported by the BTJ for oligodendrogliomas (86.7%), yet diverged regarding diffuse astrocytomas, which showed an equal prevalence in the temporal and parietal lobes (22.7%) after the frontal region.³⁶ Furthermore, our data showed a temporal lobe predominance for high-grade cases, contrasting with UK-based and Istanbul University studies that identified the frontal lobe as the primary site for glioblastoma (24.9% and predominant, respectively).³⁴ Regarding infratentorial distribution, our findings reflected the lower prevalence noted in the literature, with ependymal neoplasms being the predominant diagnosis in these regions, whereas pilocytic astrocytomas (3.8%) and standard ependymomas (3%) showed minimal frontal involvement.³⁶ These discrepancies, including the equal prevalence of oligodendroglioma in both the parietal and frontal lobes, suggest notable regional variations in glial tumor topography compared to established populations like those described by Yoshikazu et al.⁴⁸ While many global studies cite the frontal lobe as the most common site, a recent study in Turkiye for low grade gliomas and our findings show a temporal lobe lead.

Grade

In our study, more than half of the cases were classified as grade 4, while grade 3 was the least frequent. Although no changes were made in the WHO 2016 grading system itself, considering the updates introduced in the WHO 2021 classification, many IDH-wildtype grade 2 and 3 astrocytomas can now be reclassified as grade 4 glioblastoma. A study focusing on the 2016 revision of high-grade oligodendroglial tumors observed a shift from grade 3 to grade 4, accompanied by an increased incidence of glioblastoma. This shift was more pronounced in cases previously diagnosed as grade 3 oligoastrocytoma, as approximately 50% were reclassified as glioblastoma (either IDH-mutant or IDH-wildtype). Furthermore, while the 2016 WHO classification demonstrated high prognostic value, it was concluded that the distinction between grade 3 and grade 4 was not prognostic for either IDH-mutant/1p/19q-intact gliomas or IDH-wildtype gliomas; this has sparked a

debate regarding the grading of these tumors. Notably, no significant prognostic difference was found between IDH-mutant/1p/19q-intact gliomas and IDH-wildtype grade 3 and 4 gliomas.^{53,54}

Contextualizing Histopathological Findings within the WHO 2021 Classification Framework

While our findings are categorized based on the 2016 WHO Classification, it is critical to evaluate the observed clinicopathological patterns through the lens of the 2021 WHO Classification (5th Edition), which has fundamentally decoupled morphology from molecular identity. For instance, the striking frontal lobe predilection (86.7%) observed in our oligodendroglioma cases serves as a robust clinical surrogate that aligns with the current requirement for IDH mutation and 1p/19q co-deletion—the molecular hallmarks now defining this entity. Similarly, our data highlights a high prevalence of glioblastoma (59.5%), particularly in the over-50 demographic; however, under the 2021 criteria, these would be strictly stratified as IDH-wildtype, whereas high-grade cases in our younger cohorts (20–39 years) might now be reclassified as Astrocytoma, IDH-mutant, grade 4. Furthermore, the anatomical clustering of our ependymal tumors—notably the spinal concentration of myxopapillary and standard variants—mirrors the 2021 framework's move toward site-specific molecular subgroups. By mapping these histological distributions, our study provides a necessary phenotypic baseline. This morphologic-anatomical map not only validates traditional diagnostic patterns but also serves as the essential scaffolding upon which future molecular re-stratification can be built, ensuring that the transition from NOS-based reporting to integrated molecular diagnostics is grounded in established clinical trends.

Limitations

Despite the comprehensive nature of this demographic analysis, our study has several limitations that warrant consideration. The primary constraint is the absence of molecular diagnostic data—such as IDH1/2 mutation status, 1p/19q codeletion, and ATRX expression—due to technical and financial limitations during the study period. Consequently, a significant portion of our cohort was classified under the 'NOS' designation, as mandated by the WHO 2016 and 2021 criteria when molecular parameters are unavailable. Furthermore, the retrospective and single-center design of the study may limit the generalizability of our findings to the broader population. However, we believe that providing this baseline morphological and demographic data remains crucial, as it establishes a necessary framework for future research that will integrate molecular subtyping as laboratory infrastructure continues to expand.

CONCLUSION

When analyzed under the four primary categories of the 2016 WHO classification, 319 (80.8%) of the 395 glial tumor cases in our study were identified within the 'diffuse astrocytic and oligodendroglial tumors' group. Additionally, 49 cases (12.4%) were categorized as 'ependymal tumors,' while 27 cases (6.8%) were classified as 'other astrocytic tumors.' The fourth category, 'other gliomas,' was not represented in our series as no such diagnoses were rendered in our department during the study period. Because the 2016 WHO classification

is fundamentally based on molecular parameters and our cases were diagnosed without access to molecular testing, all such cases were classified under the NOS category. Due to financial constraints and time limitations, cases falling under the diffuse astrocytoma and oligodendroglial tumor headings were consolidated under the NOS designation. By establishing this comprehensive database, we aim to facilitate the integration of molecular analyses into future doctoral and residency theses within our department. Furthermore, by providing essential demographic data, our study will serve as a foundational guide for subsequent subtyping research, thereby reducing the future institutional workload. As classification and prognostic stratification become increasingly reliant on molecular features, the clinical significance of laboratory biomarker testing continues to rise. In current pathological practice, while surrogate immunohistochemical markers such as IDH1/2 and ATRX provide a practical and accessible diagnostic framework, it is essential to recognize that more advanced molecular techniques, specifically FISH, remain indispensable for the definitive assessment of 1p/19q codeletion status. The WHO 2021 classification has expanded the trend initiated in 2016 by utilizing core molecular biomarkers to define neoplasia and substantially reducing the reliance on morphological features for tumor classification. The terminology regarding tumor grading has also been simplified; while molecular features now dictate the classification, the integration of histopathological and molecular analyses determines the grade. In line with the 2021 update, our diagnostic approach for adult-type diffuse gliomas prioritized IDH1/2 mutation and 1p/19q codeletion status, categorizing cases into three distinct groups: IDH-mutant and 1p/19q-codeleted oligodendroglioma, IDH-mutant astrocytoma, and IDH-wildtype glioblastoma. In summary, we highlight that the molecular divergence between IDH-mutant and IDH-wildtype disease remains the most reliable prognostic indicator. Given the substantial discrepancy in survival between these two groups, this classification should be maintained as a priority over traditional histopathology alone. The expansion of molecular laboratory infrastructure in our country over the past decade has paved the way for deeper insights through molecular diagnostics. Nevertheless, incorporating these biomarkers into national cancer registries remains a complex undertaking requiring ongoing professional development. In the interim, considering the current limitations in some laboratory settings, the demographic profiles established in this study maintain their clinical significance as they will facilitate the categorization of future molecular cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 28.11.2016, Decision No: 2016169).

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: NBM, EÇ; Design: NBM; Control: NBM, EÇ; Resources: NBM; Data Collection and/or Processing: NBM, İS; Analysis and/or Interpretation: NBM, İS; Literature Review: NBM; Writing the Article: NBM, EÇ, İS; Critical Review: NBM, EÇ, İS.

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Adherence to prophylaxis in adults with hemophilia: the role of communication, self-infusion, and infusion timing*

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Cite this article: Demirci Z, Keklik Karadağ F, Aydın Kaynar L, et al. Adherence to prophylaxis in adults with hemophilia: the role of communication, self-infusion, and infusion timing. *J Curr Hematol Oncol Res.* 2026;4(2):40-46. doi:10.51271/JCHOR-0080

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Received: 07/03/2026

Accepted: 12/04/2026

Published: 18/05/2026

ABSTRACT

Aims: Despite advances in hemophilia management, maintaining optimal treatment adherence remains a significant challenge, particularly when access to healthcare services is limited. To evaluate treatment adherence among adult patients with hemophilia during a period of restricted access to healthcare services, with particular emphasis on the roles of health literacy and communication with healthcare professionals.

Methods: A total of 128 adult patients with moderate or severe hemophilia were enrolled in this cross-sectional study. Treatment adherence was assessed using the Validated Hemophilia Regimen Treatment Adherence Scale–Prophylaxis (VERITAS-Pro), which evaluates six domains: time, dose, plan, remember, skip, and communicate. Self-reported adherence, infusion practices, annual bleeding rate (ABR), age, and treatment-related variables were analyzed. Pearson correlation analysis and group comparisons were performed to examine associations between variables.

Results: The median age of participants was 39 years (interquartile range [IQR]: 32-47). Most patients had hemophilia A (84.4%) and severe disease (77.3%), and 82.8% reported current target joints. The mean VERITAS-Pro total score was 47.8±9.7, with 85.9% classified as adherent. High adherence was observed in timing (85.9%), planning (93.8%), remembering (93.0%), and skipping (85.9%), whereas communication represented the weakest adherence domain. Patients with higher ABR demonstrated significantly poorer communication scores ($p=0.007$). Self-infusion was associated with significantly better adherence across multiple domains, including total score, timing, and planning ($p<0.05$). Infusions administered at the beginning of the day were also associated with higher adherence. Age showed a weak, non-significant correlation with total adherence scores ($r=0.144$, $p=0.104$).

Conclusion: Structured infusion routines and self-infusion practices appear to improve treatment adherence among adult patients with hemophilia. Communication with healthcare professionals remains a critical challenge, particularly among patients with higher bleeding frequency. Interventions targeting patient–provider communication may further enhance adherence outcomes.

Keywords: Treatment adherence, self administration, health literacy, patient–provider communication, prophylaxis

*This study was presented as a poster presentation at the 15th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), held on 2-4 February 2022. The abstract was published in *Haemophilia*. 2022;28(Suppl 1):25-126. The study was also presented as a poster at the 8th Hemophilia Case-Based Education Symposium, Royal Seginus Hotel, Antalya, Türkiye, 18-20 February 2022.

INTRODUCTION

Haemophilia is an X-linked bleeding disorder characterized by bleeding into joints, muscles, and other soft tissues, which occurs either spontaneously or following trauma. In the absence of treatment, bleeding can result in significant pain, swelling, and permanent damage.¹ A joint is classified as a target joint when ≥ 3 bleeds occur in that joint over a 6-month period. It should be noted that a patient may have more than one target joint.²

The objective of replacing the missing clotting factor from exogenous sources is to regulate both the frequency and severity of bleeding episodes with the ultimate goal of preventing joint disability and life-threatening bleeding.¹

The goal of treatment is to enhance hemostasis sufficiently to prevent or control bleeding. Replacement therapy involves the intravenous infusion of FVIII or FIX concentrates.^{3,4}



Prophylactic treatment consists of intravenous infusions administered approximately two to three times per week to prevent spontaneous/traumatic bleeding.⁵ Parents of children with hemophilia who receive training are instructed in the administration of injections at home. By 12, children are encouraged to administer the injections themselves (self-infusion). For effective treatment, patients of all age groups must adhere to the treatment regimen to prevent spontaneous and/or traumatic bleeding.^{5,6} However, recurrent bleeding episodes cause chronic pain, joints dysfunctions, and musculoskeletal system deformities. In addition to supportive care measures such as rest, ice, compression, and elevation (RICE) during bleeding episodes, and physiotherapy aimed at improving physical function and protecting joint health, factor replacement therapy remains the cornerstone of haemophilia management. However, standard half-life factor therapies are associated with a significant treatment burden, including frequent infusions, difficulties with vascular access, limited reduction in haemarthrosis rates, and challenges with treatment adherence.^{7,8}

The COVID-19 pandemic has caused an unexpected impact on hemophilia healthcare delivery.⁹ The COVID-19 pandemic has significantly disrupted healthcare services, creating substantial challenges for individuals living with rare diseases such as hemophilia. According to a survey conducted by the Rare Barometer Programme of EURORDIS, approximately 90% of people with rare diseases reported interruptions in their medical care during the global crisis triggered by the SARS-CoV-2 pandemic.¹⁰ Throughout the pandemic, public health experts recommended social distancing and minimizing non-urgent face to-face examinations unless necessary. And hemophilia patients with emergencies provided healthcare access.⁹ Telemedicine had become a prevalent modality in outpatient clinic services.¹¹

Several studies have shown that low health literacy is associated with difficulty understanding recommended medical directives, increased mortality and morbidity, and treatment adherence difficulties. Limited health literacy increases the risk of developing chronic diseases, their associated complications, and disability.¹² Health literacy and health numeracy are ignored barriers to treatment adherence in haemophilia.¹³

In situations where access to healthcare is restricted, such as during public health emergencies, individuals with chronic conditions like hemophilia may need to take a more active role in managing their treatment. In this context, treatment adherence may be influenced not only by clinical factors but also by patients' level of health literacy. Therefore, this study was designed to investigate treatment adherence among adult patients with haemophilia during a period of restricted access to healthcare services, with a particular focus on self-management and communication with healthcare professionals.

METHODS

Ethics

The study was approved by Ege University Clinical Researches Ethics Committee (Date: 18.12.2020, Decision No: 20-12.1/2), and all participants provided written informed consent.

The study protocol followed the ethical requirements of the relevant institutional review bodies and was consistent with the principles established in the Declaration of Helsinki and its subsequent revisions.

Participants

This multicenter, observational, cross-sectional study was conducted at five hemophilia treatment centers between January and December 2021. The study population consisted of 128 adults with hemophilia who were required to attend treatment centers during a period of national lockdown restrictions. Inclusion criteria were a confirmed diagnosis of hemophilia A or B, age ≥ 18 years, a history of prophylactic treatment for at least two years, and the ability to provide informed consent. Patients receiving on-demand therapy and Individuals with cognitive impairments or those under the age of 18 were excluded from the study.

Clinical Data Collection

The survey consisted of two parts: (a) demographic and clinical data (i.e., ABR (annual bleeding rate), age, diagnosis, target joint, arthropathy, etc.) and (b) data regarding treatment adherence. Demographic data, including age, marital status, and educational level, were collected through patient interviews and medical records. The diagnosis of hemophilia has two types: hemophilia A (n=108) and hemophilia B (n=20). Disease severity is classified into severe, moderate, and mild. ABR and self-infusion status were obtained from patient self-report, whereas target joints, arthropathy, and prophylaxis history were extracted from medical records. Treatment adherence was assessed using two distinct approaches. First, participants were asked to subjectively indicate their adherence status. The objective was to evaluate treatment compliance from the patient's perspective. To this end, participants categorized themselves as "highly adherent," "moderately adherent," or "poorly adherent." Subsequently, the researcher asked participants to self-evaluate their compliance. Second, participants completed the Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) (Turkish Version).¹⁴ The VERITAS-Pro scale, introduced by Duncan et al.¹⁵ in 2010, consists of 24 items organized into six subscales with four items each: time, dose, plan, remember, skip, and communicate. Responses are recorded on a five-point Likert scale ranging from "always" to "never." The scoring system is structured so that lower scores reflect better treatment adherence. Possible total scores range from 24, indicating the highest adherence, to 120, indicating the lowest adherence.

Statistical Analysis

Demographic and clinical variables were summarized using descriptive statistics. Continuous data were summarized using mean \pm standard deviation or median with interquartile range (IQR) according to distributional properties, while categorical data were presented as counts and percentages. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. For normally distributed variables, comparisons between groups were performed using the Independent samples t-test or one-way ANOVA, as appropriate. For non-normally distributed variables, the Mann-Whitney U test or Kruskal-Wallis test was used. Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate. Multivariate logistic

regression analysis was performed to identify independent predictors of treatment adherence. Variables with $p < 0.10$ in univariate analysis were entered into the multivariate model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All statistical analyses were conducted using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). A two-tailed p -value < 0.05 was considered statistically significant.

RESULTS

The study included 128 adult participants, with a median age of 39 years (IQR 32-47, range 18-70). The majority had hemophilia A (84.4%), and most cases were classified as severe (77.3%). Target joints were present in 82.8% of participants. The median age at initiation of prophylaxis was 24 years (IQR 19-35). Detailed characteristics of adherent and non-adherent patients are presented in **Table 1, Figure 1**.

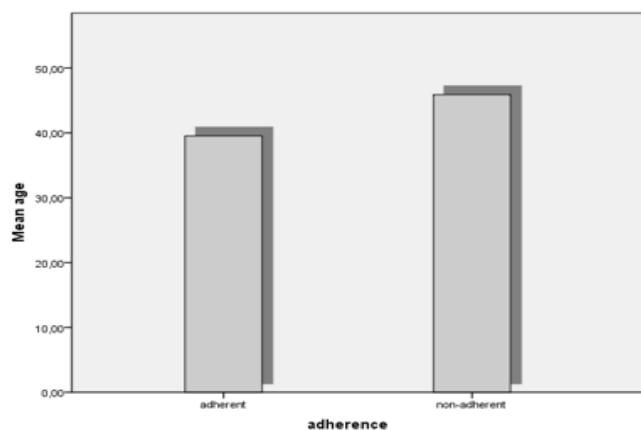


Figure 1. Graphic of the mean age of adherence and non-adherence patients

The mean overall adherence score was 47.8 ± 9.7 , with 85.9% of participants classified as adherent. High adherence rates were observed in timing, planning, remembering, and skipping domains, whereas communication was the weakest subdomain (**Table 2, Figure 2**).

Table 1. Socio-demographic and clinical characteristics of all patients, adherent patients, and non-adherent patients				
	All participant	Adherent	Non-adherent	p value
Median age, year, (min-max)	39 (19-70)	39 (19-70)	44.5 (31-63)	0.02
Marital status % (n)				0.07
Married	59.4 (76)	56.4 (62)	77.8 (14)	
Single	40.6 (52)	43.6 (48)	22.2 (4)	
Educational level, % (n)				0.75
No or basic education	2.3 (3)	2.7 (3)	0.0 (0)	
High school	62.5 (80)	61.8 (68)	66.7 (12)	
University	35.2 (45)	35.5 (39)	33.3 (6)	
Occupational status, % (n)				0.42
Work	65.6 (84)	66.4 (73)	61.1 (11)	
No work	34.4 (44)	33.6 (37)	38.9 (7)	
Diagnosis, % (n)				0.48
Hemophilia A	84.4 (108)	85.5 (94)	77.8 (14)	
Hemophilia B	15.6(20)	14.5 (16)	22.2 (4)	
Disease severity, % (n)				0.19
Severe	77.3 (99)	79.1 (87)	66.7 (12)	
Moderate	22.7 (29)	20.9 (23)	33.3 (6)	
Target joint, % (n)				0.13
Yes	82.8 (106)	80.9 (89)	94.4 (17)	
No	17.2 (22)	19.1 (21)	5.6 (1)	
Arthropathy, % (n)				0.23
Yes	85.9 (110)	84.5 (93)	94.4 (17)	
No	14.1 (18)	15.5 (17)	5.6 (1)	
Self-administration of the drug, % (n)				0.04
Self-infusion	82.8 (106)	86.4 (95)	61.1 (11)	
Family member	9.4 (12)	8.2 (9)	16.7 (3)	
Health worker	7.8 (10)	5.5 (6)	22.2 (4)	
Time for prophylaxis, % (n)				0.01
When starting the day	43.8 (56)	48.2 (53)	16.7 (3)	
At his convenience	42.2 (54)	37.3 (41)	72.2(13)	
Before bed	14.1 (18)	14.5 (16)	11.1 (2)	
Where does a patient infuse factor? % (n)				0.04
At home	90.6 (116)	92.7 (102)	77.8 (14)	
At hospital	7.8 (10)	5.5 (6)	22.2 (4)	
At work	1.6 (2)	1.8 (2)	0.0 (0)	
Annual bleeding rate (ABR), % (n)				0.3
No bleeding	36.7 (47)	39.1 (43)	22.2 (4)	
1-5	53.1 (68)	51.8 (57)	61.1 (11)	
>5	10.2 (13)	9.1 (10)	16.7 (3)	
Patient perspective , % (n)				<0.001
High adherent	57.8 (74)	65.5 (72)	11.1 (2)	
Moderate adherent	36.7 (47)	34.5 (38)	50.0 (9)	
Poor adherent	5.5 (7)	0.0 (0)	38.9 (7)	

Min: Minimum, Max: Maximum

Table 2. VERITAS-Pro total scores and subscales scores

	Mean±SD	Median (min-max)	Adherent % (n)	Non-adherent % (n)
Total score	47.8±9.7	46 (36-99)	85.9 (110)	14.1 (18)
Time	7.6±3.2	7 (4-20)	85.9 (110)	14.1 (18)
Dose	7±3.2	6 (4-20)	54.7 (70)	45.3 (58)
Plan	5.06±2.5	4 (3-15)	93.8 (120)	6.3 (8)
Remember	7.4±2.1	7 (3-13)	93.0 (119)	7.0 (9)
Skip	7.0±3.3	6 (4-20)	85.9 (110)	14.1 (18)
Communicate	13.7±2.5	14 (5-17)	7.8 (10)	92.2 (118)

SD: Standard deviation, Min: Minimum, Max: Maximum

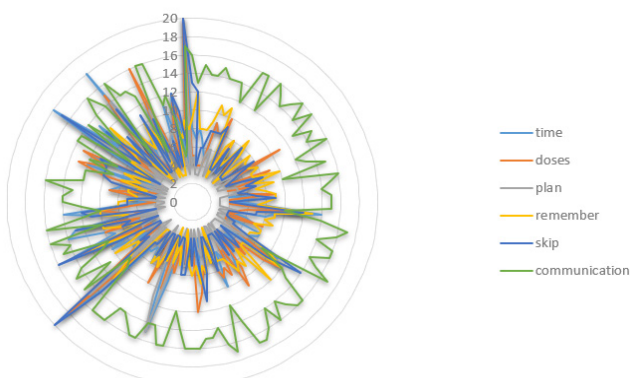


Figure 2. VERITAS-Pro subscales radar graphics
 Note: The communicate domain shows the highest variability, whereas plan and remember subscales appear more stable across participants.

No significant differences were found across ABR categories for most adherence domains ($p>0.05$); however, communication differed significantly ($p=0.007$), with poorer adherence observed in patients with higher ABR (Table 3).

Self-infusion was associated with significantly better adherence across several domains, including total score, timing, planning, remembering, and skipping ($p<0.05$). No significant differences were observed for dose or communication domains (Table 3).

Morning infusions were associated with higher adherence in total, timing, planning, and skipping domains ($p<0.05$), suggesting that structured routines may facilitate better adherence. Communication remained the lowest-scoring domain regardless of infusion timing, indicating persistent challenges in patient-provider interaction.

Patient-reported adherence measures and VERITAS-Pro scores are presented in Table 4. Non-adherent patients had higher VERITAS-Pro scores, reflecting poorer adherence. Although adherence scores tended to increase with age, the correlation between age and adherence was weak and not statistically significant ($r=0.144$, $p=0.104$). Similarly, no significant differences were observed across age groups ($p=0.219$) (Table 5), suggesting that age alone may not be a strong determinant of adherence in this cohort.

Table 3. Comparison of VERITAS-Pro adherence subscores according to bleeding frequency, self-infusion status, and time of infusion

	No bleeding (n)		Annual bleeding rate (1-5) (n)		Annual bleeding rate (>5) (n)		p-value
	Adherent	Non adherent	Adherent	Non adherent	Adherent	Non adherent	
Total score	43	4	57	11	10	3	0.313
Time	44	3	56	12	10	3	0.143
Dose	26	21	39	29	5	8	0.453
Plan	46	1	63	5	11	2	0.187
Remember	42	5	64	4	13	0	0.358
Skip	45	2	56	12	9	4	0.187
Communicate	0	47	9	59	1	12	0.007
	Self-infusion (n)		Non-self-infusion (n)		p-value		
	Adherent	Non-adherent	Adherent	Non-adherent			
Total score	95	11	15	7	0.016		
Time	96	10	14	8	0.003		
Dose	60	46	10	12	0.235		
Plan	103	3	17	5	0.004		
Remember	101	5	18	4	0.047		
Skip	95	11	15	7	0.016		
Communicate	8	98	2	20	0.541		
	When starting the day (n)		At his convenience (n)		Before bed (n)		p-value
	Adherent	Non adherent	Adherent	Non adherent	Adherent	Non adherent	
Total score	53	3	41	13	16	2	0.017
Time	53	3	41	13	16	2	0.017
Dose	33	23	27	27	10	8	0.641
Plan	56	0	47	7	17	1	0.019
Remember	54	2	48	6	17	1	0.292
Skip	53	3	42	12	15	3	0.037
Communicate	5	51	5	49	0	18	0.411

Table 4. Veritas-Pro adherence score of hemophilic-specific characteristics

	Veritas -Pro total score and subscale score (mean±SD)						
	Total score	Time	Dose	Plan	Remember	Skip	Communicate
Self-infusion							
Yes	46.6±6.9	7.1±2.5	6.7±2.7	4.7±2.01	7.3±2.02	6.5±2.6	13.9±2.5
No	54.1±16.9	9.7±5.06	8.1±4.7	6.4±4.2	7.7±2.8	9.0±5.3	13.0±16.9
Target joint							
Yes	48.9±10.1	7.8±3.3	7.2±3.3	5.2±2.7	7.5±2.2	7.3±3.5	13.6±2.6
No	42.8±4.8	6.3±2.3	5.8±2.2	4.3±1.3	6.6±1.7	5.4±1.6	14.2±1.9
ABR							
No bleeding	46.2±6.4	6.6±2.6	6.7±2.4	4.3±2.02	7.7±2.1	6.3±2.08	14.4±1.6
1-5	47.7±8.7	7.9±3.1	6.8±3.1	5.2±2.5	7.2±2.2	7.1±3.3	13.2±2.9
>5	54.6±18.9	9.4±5.04	8.7±5.08	8.7±5.08	7.1±2.03	8.8±5.7	14.0±2.5
Where does he infuse factor?							
At home	47.06±8.5	7.3±2.95	6.8±3.0	4.9±2.3	7.3±2.1	6.6±2.8	13.9±2.4
At hospital	57.6±17.1	11.3±4.6	8.1±5.1	7.3±4.2	8.3±3.09	11.1±5.4	11.5±2.2
At work	47.0±0.0	4.0±0.0	10.0±0.0	3.0±0.0	8.0±0.0	10±0.0	12.0±0.0
Time for prophylaxis							
When starting the day	44.5±5.6	6.1±2.05	6.5±2.5	4.9±1.6	6.8±2.1	6.1±2.2	13.9±2.6
At his convience	50.1±10.9	8.8±3.6	7.3±3.5	5.2±3.3	7.8±2.1	7.6±3.9	13.2±2.5
Before bed	51.4±12.8	8.6±3.4	7.3±3.8	4.6±2.5	8.0±1.9	7.8±3.8	14.9±1.8
Perspective							
High adherent	44.1±5.09	6.1±1.8	6.1±2.4	4.5±1.6	7.02±1.9	5.7±2.08	14.5±2.04
Modarate adherent	49.9±7.9	8.7±2.9	7.2±2.6	5.1±2.7	7.8±2.2	7.7±3.1	13.2±2.3
Poor adherent	73.1±16.5	15.4±3.5	14.0±4.7	10.1±4.5	8.8±2.8	15.0±3.8	9.7±3.5

SD: Standard deviation, ABR: Annual bleeding rate

Table 5. Descriptive statistics of Veritas-Pro total score by age groups

Age group	Mean (SD) (Veritas-Pro score)	% (n)	p value
18-29 years	44.57 (4.03)	16.4 (21)	0.219
30-40 years	47.29 (9.96)	38.3 (49)	
41-50 years	49.79 (11.45)	26.6 (34)	
51 and above	49.33 (9.90)	18.8 (24)	
Total	47.89 (9.76)	100 (128)	

SD: Standard deviation

DISCUSSION

The present study demonstrated generally high levels of treatment adherence among adult patients with haemophilia, with most participants showing satisfactory adherence across the VERITAS-Pro subdomains. However, adherence was suboptimal in the communication domain. In addition, adherence tended to decline with increasing age. These findings highlight the importance of effective patient-provider communication and the influence of age-related factors on adherence behaviour. In comparison, Mokhtar et al.¹⁶ reported a mean adherence score of 30.0 among 103 patients with severe haemophilia A and B (mean age, 33), suggesting relatively better adherence in our study population. In another study by Guasch et al.,¹⁸ the mean VERITAS-Pro score was 43, with 17% of patients classified as non-adherent, which is consistent with our findings. Similarly, Cheung et al.¹⁷ reported lower adherence in the “communication” and “time” subscales. These findings collectively support the observation that communication is a particularly vulnerable domain of adherence across different populations.^{17,18}

However, some studies have reported lower levels non-adherence among patients receiving prophylactic treatment, indicating generally satisfactory adherence. Similar to previous report, adherent patients had substantially lower VERITAS-Pro scores compared with non-adherent

individuals, with the latter showing particularly poor results in the dosing, planning, and communication subscales.^{17,19,20}

It was very well known that acceptance of the disease significantly improves adherence. After 12 months of study implementation, significant improvements were observed in total scores and four subscales (“time,” “remember,” “skip,” and “communication”).²¹ In hemophilia treatment, achieving zero bleeds remains a key therapeutic goal. Although this target is not always attainable with standard therapies, it has been reported in several studies. In our cohort, patients with higher treatment adherence tended to have lower ABRs, suggesting a beneficial relationship between adherence and clinical outcomes. Similarly, Mokhtar et al.¹⁶ reported significantly lower bleeding rates among adherent patients compared to non-adherent individuals. These findings further support the importance of adherence in reducing bleeding burden in patients with haemophilia. Effective communication and continuous contact between haemophilia teams and patients have been shown to play a vital role in sustaining adherence and preventing bleeds. Maintaining these close relationships is particularly important, as evidence suggests that regular follow-up and multidisciplinary engagement contribute positively to clinical outcomes, even in resource-limited settings.²²

Participants who adhered to prophylaxis infusions at appropriate times tended to experience fewer bleeding episodes and demonstrated better overall adherence. This finding is consistent with the study by Hoefnag et al.,²¹ which reported improvements in adherence following a structured training program, including increased adherence to the “correct time” for infusions at 12 months (p=0.01).

Liu et al.²³ reported that patients with haemophilia A face multiple barriers to prophylactic care, including limited knowledge of self-infusion and insufficient support in primary care. In contrast, a high proportion of patients in our cohort were able to perform self-infusion, suggesting better

adaptation to home-based treatment. This may be attributed to structured patient education and the involvement of specialized haemophilia nurses, which likely contribute to improved treatment adherence. Previous reports have shown relatively low adherence rates for infusion frequency, with better adherence observed in younger children whose treatment is managed by their parents. Among individuals who self-infuse, adherence levels assessed by the VERITAS-Pro have shown moderate adherence overall. These findings highlight the variability in adherence patterns and underscore the potential influence of age and caregiver involvement on treatment adherence.²⁴

Although our study did not identify a statistically significant relationship between age and treatment adherence, the mean age of non-adherent patients was found to be higher compared to adherent patients. Numerous studies in the literature have demonstrated that age is one of the most critical factors influencing treatment adherence. Young children and elderly individuals are often dependent on caregivers for appropriate medical care, while adolescents, young adults, and middle-aged adults are typically more independent. However, adolescents and young adults are at particularly high risk for discontinuing prophylaxis and exhibiting poor adherence to treatment protocols. Consistent with our findings, a previous study also reported no significant age-related differences in adherence levels.^{20,25}

In this study, the timing of factor infusion emerged as an important determinant of treatment adherence. Patients who infused at the beginning of the day demonstrated better adherence across several domains, whereas those who infused at their convenience showed lower adherence, particularly in timing and skipping. Communication with healthcare providers was also identified as a key area requiring improvement, as non-adherence was most pronounced in this domain. These findings highlight the importance of structured infusion routines and effective patient-provider communication in optimizing adherence. Given the well-established relationship between adherence and improved clinical outcomes, strengthening these factors may contribute to better disease management and quality of life.¹⁹

This multicenter study, conducted during the COVID-19 pandemic, offers a unique perspective on treatment adherence in adults with hemophilia under healthcare access constraints. The use of the validated Turkish VERITAS-Pro scale enabled a comprehensive assessment across six adherence domains. Subgroup analyses by self-infusion, infusion timing, and bleeding frequency provided nuanced insights. Notably, identifying “communication” as the weakest domain highlights a key area for clinical intervention. The high rate of self-infusion also underscores the value of patient education and structured training.

Limitation

The study's cross-sectional design limits causal inference. The sample may be affected by selection bias, as only patients who accessed care during the lockdown were included. Adherence was partly self-reported, introducing potential recall and social desirability biases. Relevant variables such as psychosocial or socioeconomic factors were not assessed, and

the absence of longitudinal data restricts evaluation of long-term adherence trends.

CONCLUSION

This study provides valuable insights into the predictors of clinical outcomes in patients with chronic bleeding disorders, particularly hemophilia. Age was found to be a significant predictor, while self-infusion status significantly improved adherence and clinical outcomes. These findings highlight the importance of patient empowerment through self-management strategies and consistent treatment regimens. However, the lack of significance for diagnosis-age and recent treatment modifications suggests that other factors, such as genetic predispositions and psychosocial variables, may play a more prominent role in determining long-term clinical outcomes. Further research is necessary to explore these factors and refine predictive models for personalized treatment approaches. Self-infusion training and patient-centered communication strategies are essential to improving treatment adherence in hemophilia, a chronic condition. Educational programs that encourage individuals to take responsibility for their own treatment management can enhance adherence, especially during pandemics or in rural areas where access to healthcare is limited. Adopting communication methods aligned with patients' health literacy and integrating digital platforms (e.g., teleconsultation, reminder apps, virtual education) may further improve treatment engagement. In clinical settings, these strategies play a vital role not only in managing hemophilia but also in improving long-term outcomes in the care of chronic diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by Ege University, Clinical Researches Ethics Committee (Date: 18.12.2020, Decision No: 20-12.1/2).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

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: ZD, FKK, LAK, AAI, FŞ; Design: ZD, FKK, LAK, AAI, FŞ; Control: ÖM, MSI, FŞ; Resources: ZD, ÖM, SMI,

MSI, MK; Data Collection and/or Processing: ZD, FKK, LAK, AAI, SMI, MK; Analysis and/or Interpretation: ZD, FKK, MK; Literature Review: ZD, FKK, SM; Writing the Article: ZD, FKK; Critical Review: ÖM, MSI, FŞ.

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CD34⁺ cell dose as a determinant of engraftment kinetics after autologous stem cell transplantation in lymphoma

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Cite this article: Sarıcı A, Erkurt MA, Kuku İ, et al. CD34⁺ cell dose as a determinant of engraftment kinetics after autologous stem cell transplantation in lymphoma. *J Curr Hematol Oncol Res.* 2026;4(2):47-52. doi:10.51271/JCHOR-0081

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Received: 06/03/2026

Accepted: 22/04/2026

Published: 18/05/2026

ABSTRACT

Aims: Lymphomas are heterogeneous hematologic malignancies for which autologous hematopoietic stem cell transplantation (ASCT) remains an important therapeutic option in relapsed or refractory disease. In addition to patient- and disease-related factors, graft-related parameters—particularly the infused CD34⁺ cell dose—play a critical role in hematopoietic recovery after ASCT. This study aimed to evaluate post-transplant engraftment and long-term survival outcomes in patients with Hodgkin and non-Hodgkin lymphoma according to infused CD34⁺ cell dose.

Methods: Demographic characteristics, primary diagnosis, infused CD34⁺ cell dose, neutrophil and platelet engraftment times, 1-year mortality, and 5-year survival were retrospectively obtained from hospital electronic records. Patients were stratified into two groups based on infused CD34⁺ cell dose: 2-5×10⁶/kg and >5×10⁶/kg. Engraftment times and survival outcomes were compared between groups.

Results: A total of 165 patients were included (2-5×10⁶/kg, n=67; >5×10⁶/kg, n=98). Baseline characteristics, including age, sex, and lymphoma subtype, were comparable between groups. Neutrophil and platelet engraftment times were significantly longer in the 2-5×10⁶/kg group than in the >5×10⁶/kg group (p<0.001 for both). In the overall cohort, CD34⁺ cell dose was negatively correlated with engraftment times. However, no significant differences were observed in 1-year mortality or 5-year survival between groups.

Conclusion: Adequate CD34⁺ cell dosing is essential for rapid hematopoietic recovery after ASCT, whereas higher doses do not appear to confer additional long-term survival benefit.

Keywords: Lymphoma, autologous hematopoietic stem cell transplantation, CD34⁺ cell, engraftment, survival

INTRODUCTION

Lymphomas originate from cells that normally differentiate into T lymphocytes or B lymphocytes. Hodgkin lymphoma (HL) is a lymphoid neoplasm characterized by the presence of Reed–Sternberg cells. Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of hematologic malignancies arising from B-cell or T-cell precursors, mature B or T lymphocytes, or natural killer (NK) cells, encompassing distinct histological subtypes. Diffuse large B-cell lymphoma (DLBCL), the most common subtype of NHL, is the most frequently diagnosed lymphoid malignancy worldwide and accounts for approximately 30% of all lymphomas.^{1,2}

In the United States, an estimated 89,070 new cases of lymphoma were diagnosed in 2025, with over 20,540 lymphoma-related deaths reported during the same year.³ Lymphoma management involves chemotherapy,

radiotherapy, combinations of chemoradiotherapy, and autologous hematopoietic stem cell transplantation (ASCT).

Chemotherapy remains the standard first-line treatment for both Hodgkin and NHLs. In patients with chemorefractory lymphoma, ASCT is the preferred therapeutic modality, as it has been shown to confer a progression-free survival (PFS) benefit.^{4,5}

ASCT is a classic treatment option for patients with hematological malignancies.⁶ Factors influencing the success of ASCT, which is also applied in patients with Hodgkin and NHL, have been identified.⁷ Age, performance status, organ dysfunction, central nervous system (CNS) involvement, bone marrow involvement are known to affect ASCT outcomes.⁸⁻¹⁰ The dose of transplanted CD34⁺ cells is also known to influence clinical outcomes.¹¹



High circulating CD34⁺ cell counts are known to be associated with shorter hospital stays, a reduced incidence of febrile neutropenia, and shorter neutrophil and platelet engraftment times.^{12,13} Previous studies in the literature have demonstrated that higher circulating CD34⁺ cell counts are associated with improved overall survival (OS) in patients undergoing ASCT.¹⁴

The primary aim of our study is to contribute to the literature by presenting the results of our Hodgkin and NHL patients who underwent ASCT at our center, based on their CD34⁺ cell count.

METHODS

Following approval by the İnönü University Health Sciences Scientific Researches Ethics Committee (Date: 16.11.2021, Decision No: 2021/2687), patient data were retrospectively collected. The study population consisted of patients who underwent ASCT at the İnönü University Bone Marrow Transplantation Unit. All consecutive lymphoma patients undergoing ASCT during the study period were included. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

Patients' age, gender, primary disease, pre-transplant infused CD34⁺ cell count, neutrophil and platelet engraftment times, 1-year mortality, and 5-year survival rates were retrospectively obtained from the hospital automation system and our records.

An infused CD34⁺ cell dose of $\geq 2 \times 10^6$ cells/kg is generally accepted as the minimum required threshold for ASCT. This dose is considered adequate for successful engraftment and timely hematopoietic recovery. In contrast, lower CD34⁺ cell doses are associated with delayed neutrophil and platelet engraftment, greater transfusion needs, and longer hospital stay.

All patients were mobilized using G-CSF-based protocols. CD34(+) cell counts were measured by flow cytometry according to institutional laboratory standards. Collected cells were cryopreserved with 10% DMSO and stored at -80°C . Before infusion, the bags were rapidly thawed in a 37°C water bath and reinfused on day 0 following conditioning.

Neutrophil engraftment was defined as an absolute neutrophil count $>0.5 \times 10^9/\text{L}$ for three consecutive days without granulocyte colony-stimulating factor (G-CSF) support. Platelet engraftment was defined as a platelet count $>20 \times 10^9/\text{L}$ for three consecutive days without platelet apheresis support.

Patients were divided into two groups based on CD34⁺ cell count: $2-5 \times 10^6/\text{kg}$ and $>5 \times 10^6/\text{kg}$. Neutrophil and platelet engraftment times, 1-year mortality, and 1-year survival rates were compared between the groups.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as number and percentage (n, %)

for categorical variables, and as mean \pm standard deviation (mean \pm SD) and median (minimum–maximum) for continuous variables.

For comparisons between two groups, the Independent t-test was used for parametric data, while categorical variables were compared using the Pearson Chi-square test. Survival outcomes among clinical groups were analyzed using the Kaplan–Meier method. A p value <0.05 was considered statistically significant.

Cox proportional hazards regression analysis was conducted for OS, and binary logistic regression analysis was performed for 1-year mortality. Variables considered in the multivariable models included age, sex, lymphoma subtype (HL vs. NHL), and CD34⁺ cell dose group ($2-5 \times 10^6/\text{kg}$ vs. $>5 \times 10^6/\text{kg}$). Where available, clinically relevant covariates were also evaluated. Cox proportional hazards regression analysis to estimate the effect of infused CD34⁺ cell dose group on OS.

RESULTS

A total of 165 patients were included in the study. Patients were stratified into two groups according to the infused CD34⁺ cell dose prior to hematopoietic stem cell transplantation: 2-5 (n=67) and >5 (n=98). The mean age of the study population was 46.00 ± 15.78 years (mean \pm SD). **Table 1** presents a comparison of a total of 165 patients stratified into two groups according to CD34⁺ cell count: 2-5 (n=67) and >5 (n=98). One patient had unavailable follow-up data for the 1-year mortality assessment and was therefore excluded from this specific analysis.

The mean age was comparable between the groups, with no statistically significant difference observed (p=0.386). Similarly, no significant difference was found in terms of sex distribution between the groups (p=0.520). There was also no statistically significant difference between the CD34⁺ groups with respect to primary disease type (HL vs. NHL) (p=0.262).

In contrast, the neutrophil engraftment time was significantly longer in the CD34⁺ 2-5 group compared with the >5 group (13.44 ± 5.23 days vs. 10.64 ± 2.14 days; p<0.001). Likewise, platelet engraftment occurred later in the CD34⁺ 2-5 group, and this difference was also statistically significant (18.08 ± 13.89 days vs. 11.81 ± 4.28 days; p<0.001).

With regard to one-year survival, no statistically significant difference was identified between the groups (p=0.693). These findings suggest that a higher CD34⁺ cell count may be associated with a shorter hematopoietic engraftment time; however, it does not appear to have a significant impact on short-term survival.

The revised analyses demonstrated that although higher infused CD34⁺ cell dose was significantly associated with faster neutrophil and platelet engraftment, it was not identified as an independent predictor of OS or 1-year mortality after adjustment for confounding factors.

According to the correlation analysis between CD34⁺ cell count and engraftment times presented in **Table 2**, a statistically significant negative correlation was observed

Table 1. Comparison of sociodemographic and clinical variables between CD34+ groups

Variables	Total (n=165)	CD34 (+) cells 2-5 (n=67)	CD34 (+) cells >5 (n=98)	P
Age				
Mean±SD	46.00±15.78	47.29±14.52	45.12±16.60	0.386 ^a
Median (min-max)	47.0 (19-78)	49.0 (19-72)	43.0 (19-78)	
Sex, n (%)				
Female	52 (31.5)	23 (34.3)	29 (29.8)	0.520 ^b
Male	113 (68.5)	44 (65.7)	69 (70.4)	
Primary disease, n (%)				
HL	55 (33.3)	19 (28.4)	36 (36.7)	0.262 ^b
NHL	110 (66.7)	48 (71.6)	62 (63.3)	
1-year mortality				
No	86 (52.4)	34 (51.5)	52 (53.1)	0.846 ^b
Yes	78 (47.6)	32 (48.5)	46 (46.9)	
Neutrophil engraftment (days)				
Mean±SD	11.72±3.88	13.44±5.23	10.64±2.14	<0.001 ^a
Median (min-max)	11.0 (8.0-30.0)	12.0 (8.0-30.0)	10.0 (8.0-25.0)	
Platelet engraftment (day)				
Mean±SD	14.21±9.68	18.08±13.89	11.81±4.28	<0.001 ^a
Median (min-max)	12.0 (6.0-93.0)	14.0 (6.0-93.0)	11.0 (6.0-30.0)	
Survival (1 year)				
Mean±SD	19.10±20.36	18.34±20.87	19.63±20.09	0.693 ^a
Median (min-max)	104(0.13-85.50)	13.8 (0.73-83.87)	11.4 (0.13-85.50)	

SD: Standard deviation, Min: Minimum, Max: Maximum, HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma, a: Independent t-test, b: Pearson Chi-Square test, p<0.05 statistically significant

between CD34 level and neutrophil engraftment time in the overall patient cohort (n=165) (r=-0.265; p=0.001). Similarly, a significant negative correlation was identified between CD34 level and platelet engraftment time (r=-0.250; p=0.002). These findings indicate that increasing CD34+ cell counts are associated with shorter engraftment times.

Table 2. Relationship between CD34+ cells and engraftment

		Total (n=165)	CD34 (+) 2-5 (n=67)	CD34 (+) >5 (n=98)
		CD34	CD34	CD34
Neutrophil engraftman	r	-.265**	-.262**	-.091
	p	0.001	0.045	0.383
Platelet engraftman	r	-.250**	-.079	-.198
	p	0.002	0.553	0.054

Pearson correlation test

In subgroup analyses, a significant negative correlation between CD34 and neutrophil engraftment time was also observed in the CD34+ 2-5 group (r=-0.262; p=0.045); however, the association with platelet engraftment time was not statistically significant (p=0.553). In the CD34+ >5 group, no statistically significant correlation was found between CD34 level and either neutrophil or platelet engraftment times (p=0.383 and p=0.054, respectively).

These results suggest that increases in CD34+ cell count have a pronounced impact on engraftment time particularly within the lower CD34 range, whereas this relationship appears to attenuate at higher CD34 levels.

When OS outcomes were evaluated according to CD34 level in **Table 3**, the 2-year survival rate in the entire patient cohort was 53.6%, the 5-year survival rate was 33.0%, and the median survival time was 35.46 months (95% CI: 10.52–60.41). In the CD34+ 2-5 group, the 2-year and 5-year survival rates were 56.2% and 38.6%, respectively, with a median survival time of 50.30 months (95% CI: 11.86–88.73). In the CD34+ >5 group, the corresponding 2-year and 5-year survival rates were 52.1% and 30.2%, respectively, and the median survival time was calculated as 29.66 months (95% CI: 6.90–52.42) (**Figure 1, 2**).

Table 3. Patient OS comparisons

Variables	2 year %	5 year %	Median, month (95% CI)	p
General	53.6	33.0	35.46 (10.52-60.41)	
CD34+ cells				
2-5	56.2	38.6	50.30 (11.86-88.73)	0.791
>5	52.1	30.2	29.66 (6.90-52.42)	

OS: Overall survival, CI: Confidence interval, Kaplan-Meier, Log-rank test, p<0.05 statistically significant.

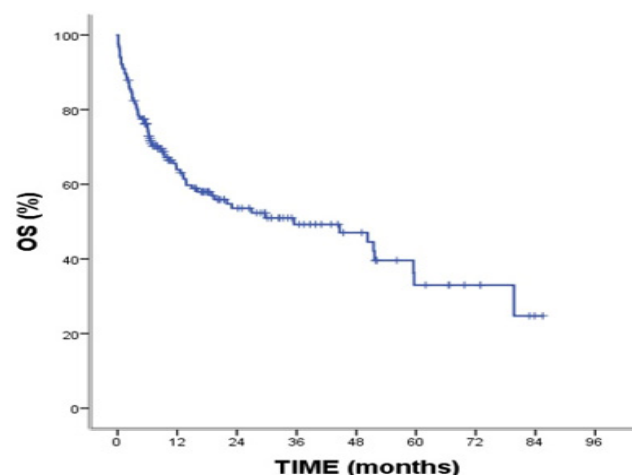


Figure 1. The Kaplan-Meier curve illustrates OS in the study population OS: Overall survival

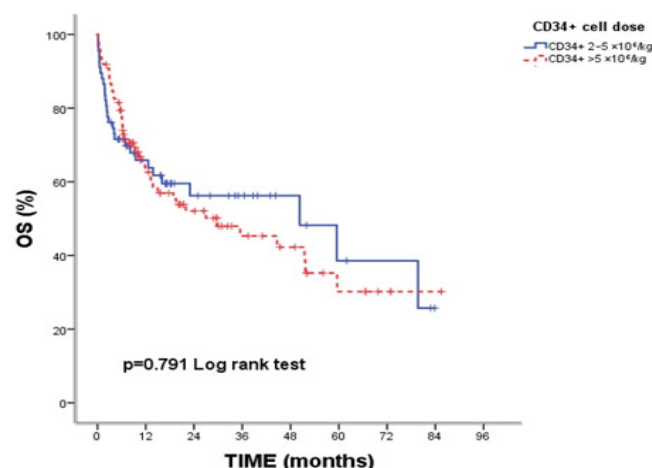


Figure 2. Kaplan-Meier curves depicting OS of patients stratified into two groups according to CD34+ cell dose OS: Overall survival

However, no statistically significant difference in OS was observed between the groups (log-rank $p=0.791$). These findings indicate that although numerical differences in survival outcomes exist according to CD34 level, these differences do not reach statistical significance.

The $>5 \times 10^6/\text{kg}$ group was not significantly associated with OS compared with the $2-5 \times 10^6/\text{kg}$ group (HR: 1.08, 95% CI: 0.68–1.72, $p=0.749$).

DISCUSSION

In this cohort of 165 patients stratified by infused CD34(+) cell dose into $2-5 \times 10^6/\text{kg}$ and $>5 \times 10^6/\text{kg}$ groups, baseline characteristics were comparable between groups. In contrast, hematopoietic recovery was significantly delayed in the CD34(+) $2-5 \times 10^6/\text{kg}$ group, with longer neutrophil engraftment and platelet engraftment times. One-year survival did not differ between groups. Correlation analyses in the entire cohort demonstrated significant negative associations between CD34(+) cell dose and both neutrophil and platelet engraftment times, indicating faster engraftment with higher CD34(+) cell doses. Subgroup analyses showed that this relationship persisted primarily in the lower CD34(+) range: in the $2-5 \times 10^6/\text{kg}$ group, CD34(+) dose correlated negatively with neutrophil engraftment but not with platelet engraftment, whereas no significant correlations were observed in the $>5 \times 10^6/\text{kg}$ group.

OS analyses revealed no significant differences according to CD34(+) cell dose. In the entire cohort, 2-year and 5-year OS rates were 53.6% and 33.0%, respectively, with a median OS of 35.46 months. In the CD34(+) $2-5 \times 10^6/\text{kg}$ group, 2-year and 5-year OS rates were 56.2% and 38.6%, with a median OS of 50.30 months, while corresponding rates in the CD34(+) $>5 \times 10^6/\text{kg}$ group were 52.1% and 30.2%, with a median OS of 29.66 months. Despite these numerical differences, OS did not differ significantly between groups. The lack of an OS benefit despite faster engraftment may be explained by the fact that long-term survival after ASCT is mainly determined by disease biology, remission status, relapse, and treatment-related complications rather than engraftment speed alone. The stronger association at lower CD34⁺ doses likely reflects a threshold effect: when the stem cell dose is near the minimum required level, small increases may significantly shorten engraftment time, whereas higher doses provide diminishing benefit. Lymphomas differ in prior therapies, marrow reserve, and prognosis. Analyzing them together may mask subgroup-specific effects.

Collectively, these findings suggest that higher CD34(+) cell doses are associated with faster hematopoietic engraftment—particularly within the lower dose range—without conferring a measurable survival advantage. Previous studies have demonstrated that a CD34⁺ cell dose of $\geq 2 \times 10^6$ cells/kg is generally sufficient for successful engraftment and acceptable recovery times, suggesting that targeting substantially higher CD34⁺ doses may not always provide additional clinical benefit.¹³

In the study by Balint et al.¹⁵ investigating patients with HL and multiple myeloma (MM), multivariate analysis of factors affecting survival demonstrated that a higher infused

CD34⁺ cell dose and better pre-ASCT performance status were independently associated with superior post-transplant event-free survival (EFS) and OS. In our study, OS analyses revealed no significant differences according to CD34(+) cell dose.

In the retrospective study by Hassan et al.,¹⁶ patients were stratified into three groups according to the pre-transplant infused CD34⁺ cell dose ($<5.0/\geq 5.0 \times 10^6/\text{kg}$ and $<7.0/\geq 7.0 \times 10^6/\text{kg}$). A statistically significant inverse association was reported between platelet engraftment and pre-transplant CD34⁺ cell dose. Furthermore, multivariate analysis identified CD34⁺ cell dose ($<7.0/\geq 7.0 \times 10^6/\text{kg}$; $p=0.002$) as an independent predictor of platelet engraftment.

In the single-center retrospective study by Lutfi et al.,¹⁷ a low infused CD34⁺ cell dose ($<3 \times 10^6/\text{kg}$; $p=0.0012$) and a low pre-transplant platelet count ($<150 \times 10^3/\mu\text{L}$; $p=0.0027$) were reported to be significantly associated with delayed engraftment. Avery et al.¹⁸ also reported that higher CD34⁺ cell counts were associated with increased rates of sustained engraftment and more rapid neutrophil recovery. Similarly, in our study, negative associations between CD34(+) cell dose and both neutrophil and platelet engraftment times, indicating faster engraftment with higher CD34(+) cell doses.

Yamaguchi et al.¹⁹ reported a multicenter retrospective study including 144 patients with B-cell non-HL who underwent ASCT. During a median follow-up of 930 days, platelet engraftment was successfully achieved in 139 patients, with a median time to platelet engraftment of 19 days. In multivariate analysis, a low transplanted CD34⁺ cell dose ($\leq 2.0 \times 10^6/\text{kg}$) was independently associated with a prolonged time to platelet engraftment following ASCT. In the study by D'Rozario et al.,²⁰ no significant difference in neutrophil engraftment was observed across different viable CD34⁺ cell counts ($p=0.545$). In contrast, a statistically significant difference in platelet engraftment was reported between patients receiving higher versus lower pre-infusion viable CD34⁺ cell doses ($p<0.001$). Our study also found a negative correlation between CD34(+) cell dose and platelet engraftment; this indicates faster adhesion at higher CD34(+) cell doses.

In the retrospective study by Sarıcı et al.,²¹ patients with NHL and HL were evaluated in three groups according to the stem cell mobilization strategy applied prior to ASCT. A statistically significant difference in CD34⁺ cell counts was observed among the groups ($p<0.001$); however, despite differences in the number of collected CD34⁺ cells, neutrophil and platelet engraftment times were similar across the three groups ($p>0.05$).

In the study by Fernandez-Sojo et al.,²² univariate analysis in the NHL cohort demonstrated that the post-thaw viable CD34⁺ cell count was significantly associated with OS. This association remained statistically significant in multivariate analysis, with the number of post-thaw viable CD34⁺ cells per kilogram retaining independent prognostic value. Infusion of more than 2×10^6 post-thaw viable CD34⁺ cells/kg was associated with improved OS ($p=0.0398$). With respect to PFS, post-thaw viable CD34⁺ cells/kg were significant in univariate analysis. In multivariate analysis, the presence of more than

2.3×10^6 post-thaw viable CD34⁺ cells/kg was independently associated with better PFS ($p=0.0048$).

Partanen et al.²³ investigated the impact of low ($<2.0 \times 10^6$ /kg) versus adequate ($\geq 2.0 \times 10^6$ /kg) infused CD34⁺ cell doses on hematologic recovery, PFS, and OS in patients with lymphoma. They reported that a low infused viable CD34⁺ cell dose was not associated with adverse PFS or OS outcomes in this patient population. Similarly, in our study, no statistically significant difference in OS was observed between the groups (log-rank $p=0.791$).

This study has several strengths. A relatively large real-world cohort of 165 patients was included to evaluate the impact of post-transplant CD34(+) cell dose. Another strength of our study is that the outcomes were assessed in patients managed at a single center and followed by the same clinicians, ensuring a more consistent clinical approach. In addition, the evaluation of both early outcomes and long-term survival increases the clinical relevance of the findings.

Limitations

This study has several limitations. First, its retrospective, single-center design limits causal inference and may introduce selection bias, thereby reducing the generalizability of the findings. Second, although the total cohort size was reasonable, the number of patients within each CD34(+) subgroup may have been insufficient to detect subtle differences in long-term survival, potentially leading to type II error. Moreover, important clinical variables that could influence engraftment kinetics and survival outcomes—including disease status at transplantation, conditioning intensity, graft source characteristics, supportive care strategies, and post-transplant complications—were not fully accounted for and may have confounded the observed associations. The inability to assess CRP levels, febrile neutropenia, and comorbidities are limitations of this study. The use of categorical CD34(+) cut-off values, rather than modeling cell dose as a continuous variable, may also have reduced sensitivity to detect nonlinear or threshold effects. Finally, the lack of detailed data on immune reconstitution and graft cellular subsets limits insight into the biological mechanisms underlying the relationship between CD34(+) cell dose and hematopoietic recovery.

CONCLUSION

In this cohort of patients undergoing autologous stem cell transplantation, higher infused CD34⁺ cell doses were associated with shorter neutrophil and platelet engraftment times, indicating a relationship with more rapid hematopoietic recovery. The inverse association between CD34⁺ cell count and engraftment duration was more apparent within the lower CD34⁺ range, while this relationship appeared to attenuate at higher cell doses. In contrast, no statistically significant differences in OS were observed between CD34⁺ groups, despite numerical variations in survival estimates. Taken together, these findings suggest that achieving an adequate CD34⁺ cell dose may be important for early post-transplant recovery, whereas increases beyond this range do not appear to be associated with clear long-term survival benefits.

ETHICAL DECLARATIONS

Ethics Committee Approval

Following approval by the İnönü University Health Sciences Scientific Researches Ethics Committee (Date: 16.11.2021, Decision No: 2021/2687).

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: AS, MAE, İK; Design: EK, İB SB; Control: AK, EH, AV; Resources: MFU, MA, OSY; Materials: AS, MAE, İK; Data Collection and/or Processing: EK, İB SB; Analysis and/or Interpretation: AK, EH, AV; Literature Review: MFU, MA, OSY; Article Writing: AS, MAE, İK; Critical review: AS, MAE, İK.

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Efficacy and safety of vincristine as salvage therapy in refractory thrombotic thrombocytopenic purpura: a single center experience

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Cite this article: Demircan V, Karakuş A, Ayyıldız MO. Efficacy and safety of vincristine as salvage therapy in refractory thrombotic thrombocytopenic purpura: a single center experience. *J Curr Hematol Oncol Res.* 2026;4(2):53-56. doi:10.51271/JCHOR-0082

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Received: 18/03/2026

Accepted: 28/04/2026

Published: 18/05/2026

ABSTRACT

Aims: Thrombotic thrombocytopenic purpura (TTP) is a life-threatening thrombotic microangiopathy caused by severe ADAMTS13 deficiency, leading to widespread microvascular thrombosis and requiring urgent therapeutic plasma exchange (TPE) and immunosuppression. Although most patients achieve remission with first-line TPE and corticosteroids, approximately 10-40% develop refractory disease requiring additional therapies. In our center, rituximab is administered in cases of plasma exchange and steroid failure. In the event of rituximab failure, vincristine is given as a third-line treatment.

Methods: We conducted a retrospective single-center study of adult patients diagnosed with TTP between 2020 and 2025. All patients received first-line daily TPE plus corticosteroids. Refractoriness was defined as failure to achieve platelet recovery or biochemical improvement after 5-7 days of therapy. Patients laboratory results were obtained from the hospital's record system.

Results: A total of 25 patients were included. First-line therapy achieved remission in 48% of patients (12/25). Among 13 refractory patients, rituximab induced remission in 2 (15%). Eleven patients subsequently received vincristine salvage therapy, of whom 9 (81.8%) achieved complete remission, accompanied by rapid platelet recovery and normalization of lactate dehydrogenase levels. Two elderly patients with severe multisystem involvement died despite salvage therapy. Overall survival for the cohort was 92%.

Conclusion: Vincristine was highly effective and well tolerated as a salvage therapy in patients with refractory TTP who failed both TPE and rituximab, achieving remission in more than 80% of cases. These findings support vincristine as a valuable therapeutic option, particularly in settings where caplacizumab or other advanced biologics are unavailable. Larger prospective studies are warranted to better define its optimal timing and comparative efficacy among emerging salvage therapies.

Keywords: Thrombotic thrombocytopenic purpura, vincristine, refractory TTP, salvage therapy, plasma exchange, rituximab, ADAMTS13 deficiency

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening thrombotic microangiopathy characterized by microangiopathic hemolytic anemia and thrombocytopenia, frequently accompanied by ischemic organ involvement, most commonly affecting the brain and kidneys.¹ TTP may be congenital or acquired; however, both forms share a common pathogenic mechanism: severe deficiency of the von Willebrand factor (VWF)-cleaving protease A Disintegrin and Metalloprotease with Thrombospondin type 1 motif, member 13 (ADAMTS13). Profound ADAMTS13 deficiency (<10%) leads to the accumulation of ultra-large VWF multimers, promoting spontaneous platelet aggregation and disseminated microvascular thrombosis.¹ If left untreated, acute TTP is associated with mortality rates approaching 90%, highlighting the need for rapid diagnosis and immediate treatment.¹

The standard first-line treatment for acquired TTP consists of daily therapeutic plasma exchange (TPE) combined

with immunosuppression, most commonly high-dose corticosteroids.^{2,3} Plasma exchange removes circulating autoantibodies and replenishes functional ADAMTS13, resulting in a marked improvement in survival, with mortality decreasing to approximately 10-20% in the modern era.¹ Although the majority of patients respond to first-line therapy, an estimated 10-40% fail to achieve adequate platelet recovery and are classified as having refractory TTP, necessitating escalation of treatment to prevent fatal outcomes.^{4,5}

Rituximab, an anti-CD20 monoclonal antibody that suppresses anti-ADAMTS13 autoantibody production through B-cell depletion, is the most widely used second-line therapy for refractory or relapsing TTP.⁶ High remission rates have been reported, particularly when rituximab is administered early in the disease course.⁶ Nevertheless, a subset of patients either does not respond to rituximab or cannot receive it due to contraindications. In such cases,



evidence guiding third-line or salvage therapies remains limited and is largely derived from small observational studies.⁷

Among traditional immunosuppressive agents, vincristine—a vinca alkaloid chemotherapeutic—has emerged as a potential salvage therapy in refractory TTP. In addition to its cytotoxic effects on rapidly dividing cells, vincristine appears to exert immunomodulatory and platelet-directed effects, including interference with platelet–VWF interactions. Small case series have reported remission rates ranging from 50% to 87% in refractory TTP, suggesting a possible therapeutic role despite the absence of randomized controlled trials.⁸

In this single-center observational study, we evaluated patients with TTP treated between 2020 and 2025, focusing on those who required vincristine as third-line salvage therapy after failure of plasma exchange, corticosteroids, and rituximab. Our aim was to assess the efficacy and safety of vincristine in refractory TTP and to contextualize its role within contemporary TTP management.

METHODS

Ethics

This study was approved by the Dicle University Ethics Committee for Non-interventional Clinical Researches (Date: 26.11.2025, Decision No: 74). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Patient Population

We conducted a retrospective, single-center analysis of adult patients diagnosed with TTP between 2020 and 2025 at Dicle University Educational Hospital. All patients fulfilled established clinical criteria for TTP, including severe thrombocytopenia (typically $<30 \times 10^9/L$), microangiopathic hemolytic anemia with schistocytes on peripheral blood smear, and absence of an alternative cause of thrombotic microangiopathy. Given the life-threatening nature of TTP, treatment was initiated immediately upon clinical suspicion without awaiting ADAMTS13 assay results.

Treatment Strategy

All patients received first-line therapy consisting of daily TPE with fresh frozen plasma replacement combined with high-dose corticosteroids. Plasma exchange was performed once daily, exchanging approximately 1-1.5 plasma volumes, and continued until remission criteria were met. Remission was defined as a sustained platelet count $>150 \times 10^9/L$ for at least two consecutive days, accompanied by clinical stabilization and improvement in hemolysis parameters. Corticosteroids were administered concurrently (prednisone 1 mg/kg/day or equivalent methylprednisolone) to suppress autoantibody production. Refractory TTP is a type of thrombotic microangiopathy that does not result in clinical improvement despite first-line treatments such as plasma exchange and steroid therapy.¹

Patients who failed to demonstrate platelet recovery or biochemical improvement after 5-7 days of daily TPE and corticosteroids were considered refractory to first-line therapy. These patients received second-line treatment with rituximab

(375 mg/m² intravenously once weekly, up to four doses), while daily plasma exchange was continued. Refractoriness was defined as failure to achieve platelet recovery or evidence of clinical deterioration despite approximately one week of therapy. Patients who initially responded but experienced an early exacerbation within 30 days of discontinuing plasma exchange were also classified as refractory.

Patients who remained refractory after rituximab therapy, or whose exacerbation was not controlled by rituximab, received vincristine as third-line salvage therapy. Due to clinical deterioration in our patients, four doses of rituximab therapy were not awaited, and treatment was switched to vincristine. Vincristine was administered intravenously at a dose of 2 mg (approximately 1.4 mg/m², capped at 2 mg) once weekly for up to three doses, depending on clinical response. Plasma exchange was continued concomitantly until remission was achieved. No additional immunosuppressive agents were introduced during this salvage phase. Unfortunately, given the retrospective nature of this study and the limitations of our dataset, we were unable to consistently collect data on these parameters across all patients. Nonetheless, we have made efforts to include available data related to the number of TPE sessions and treatment outcomes such as platelet recovery.

Data Collection and Outcomes

Data collected included patient demographics, baseline laboratory values (platelet count, lactate dehydrogenase [LDH], creatinine), number of plasma exchange sessions, and details of administered therapies. The primary outcome was clinical remission, defined as normalization of platelet count ($>150 \times 10^9/L$) with discontinuation of plasma exchange for at least 30 days. Secondary outcomes included time to remission, treatment failure, and overall survival. Treatment response was defined by platelet recovery and LDH normalization, whereas treatment failure was defined as persistent thrombocytopenia or hemolysis despite therapy, or TTP-related death.

Statistical Analysis

Given the observational nature of the study, analyses were descriptive. Continuous variables were summarized using medians and ranges, and categorical variables were reported as frequencies and percentages.

RESULTS

A total of 25 patients with TTP were included in the analysis. The median age was 41 years (range, 21-85), and 14 patients (56%) were male. At presentation, all patients exhibited severe thrombocytopenia and microangiopathic hemolysis. The median platelet count at admission was $24 \times 10^9/L$, and the median LDH level was 900 IU/L. All patients had severely reduced ADAMTS13 activity ($<10\%$) with detectable inhibitors, confirming the diagnosis of acquired immune TTP.

Treatment Response and Outcomes

All patients received first-line therapy with daily TPE and corticosteroids (Table). Twelve patients (48%) achieved remission with first-line therapy alone, with platelet recovery above $150 \times 10^9/L$ and normalization of LDH after a median of

seven plasma exchange sessions (range, 5-14). These patients required no additional therapy.

Table. Distribution of remission, refractoriness, and mortality in treated patients

Therapy line	Patients treated (n)	Remission achieved (n, %)	Refractory (needed next-line) (n)	Mortality (n)
First-line (TPE + steroids)	25	12 (48%)	13	0
Second-line (rituximab)	13 (52%)	2 (15%)	11	0
Third-line (vincristine)	11 (44%)	9 (81.8%)	–	2

TPE: Therapeutic plasma exchange

Thirteen patients (52%) were refractory to first-line treatment and received second-line rituximab. Among these patients, only two (15%) achieved remission following rituximab therapy, allowing discontinuation of plasma exchange by days 10-12 of hospitalization. The remaining 11 patients showed persistent thrombocytopenia and ongoing hemolysis despite continued plasma exchange and rituximab and were therefore escalated to third-line therapy with vincristine.

Response to Vincristine Salvage Therapy

Eleven patients received vincristine as third-line salvage therapy. Of these, nine patients (81.8%) achieved complete remission. Platelet counts increased rapidly following vincristine initiation, reaching normal levels ($>250 \times 10^9/L$) within 1-2 weeks in most responders. This was accompanied by parallel normalization of LDH levels and resolution of clinical manifestations. Plasma exchange was successfully tapered and discontinued in all responders, and remission was sustained for at least 30 days after cessation of therapy.

Two patients (18.2%) did not respond to vincristine and died from TTP-related complications. Both were elderly patients with severe multisystem involvement at presentation. One patient died from intracerebral hemorrhage in the setting of persistent severe thrombocytopenia, and the other from presumed TTP-related myocardial ischemia. No further salvage therapies were pursued due to rapid clinical deterioration. Overall survival for the cohort was 92% (23 of 25 patients) (Table).

Safety

Vincristine was generally well tolerated. Mild peripheral neuropathy occurred in two patients and transient leukopenia in two patients; both resolved without intervention. No cases of severe neurotoxicity, clinically significant myelosuppression, or treatment-limiting adverse events were observed, and vincristine was not discontinued in any patient due to toxicity.

DISCUSSION

In this single-center study, we evaluated vincristine as third-line salvage therapy in patients with refractory TTP. Our findings demonstrate that vincristine induced remission in the majority of patients who failed to respond to both first-line plasma exchange with corticosteroids and second-line rituximab, with an overall remission rate of 81.8%. This result

is clinically meaningful, as these patients had ongoing, life-threatening disease despite standard therapies.

The remission rate observed in our cohort is consistent with previously reported outcomes for vincristine in refractory or relapsed TTP, which range from 50% to 87%.⁸ Our results corroborate earlier small case series, including those by Ferrari et al.⁸ and Öngören et al.,⁹ and further support the role of vincristine as an effective salvage option in this setting. Together, these findings reinforce existing evidence that vincristine remains a viable therapeutic strategy when conventional approaches fail.

The mechanisms underlying vincristine's efficacy in TTP are likely multifactorial. In addition to its cytotoxic effects on rapidly dividing cells, vincristine may suppress autoantibody-producing immune cells, thereby facilitating recovery of ADAMTS13 activity. Experimental and clinical data also suggest a direct platelet-directed effect, with reduced platelet-VWF interactions, potentially leading to a more rapid interruption of microvascular thrombosis.¹⁰ Importantly, vincristine causes minimal bone marrow suppression at the doses used in TTP, preserving megakaryocyte function and allowing platelet recovery—an advantage over other cytotoxic agents in patients with severe thrombocytopenia.^{7,10}

In our cohort, the apparent response to rituximab was lower than that reported in other series, with remission achieved in only 15% of patients treated with rituximab as second-line therapy. This finding likely reflects the timing of rituximab administration in our practice, where it was introduced after failure of first-line therapy in patients with advanced and rapidly progressive disease. Given the delayed onset of rituximab's immunologic effects, many patients required a more rapidly acting intervention. In contrast, studies reporting higher rituximab response rates often employed early or upfront rituximab administration. Our results therefore do not diminish the role of rituximab but highlight the continued need for additional salvage strategies in severe or rapidly refractory TTP.^{4,5}

Vincristine was particularly effective in patients who had already failed rituximab, suggesting a complementary or distinct mechanism of action.⁹ The high overall survival rate of 92% in our cohort underscores the clinical impact of successful salvage therapy in this population. While some patients might eventually respond to prolonged immunosuppression, the acute and fulminant nature of TTP often precludes a “wait-and-see” approach, making timely escalation of therapy essential.⁵

Compared with other salvage options—such as cyclophosphamide, cyclosporine, splenectomy, or bortezomib—vincristine offers a favorable balance between efficacy and toxicity.² Newer agents, including caplacizumab, have demonstrated efficacy in accelerating platelet recovery and reducing exacerbations; however, access may be limited in some settings due to cost or availability.⁵ In this context, vincristine remains a practical and widely accessible option, particularly in resource-limited environments. In patients who received vincristine, clinical and laboratory improvements were observed on average after the fourth day.

The treatment was completed with three doses of vincristine, administered weekly. We observed a good response rate in our patients, but larger cohorts are needed to draw broader conclusions.

Limitations

Several limitations of this study should be acknowledged. Its retrospective design and relatively small sample size limit definitive conclusions regarding causality. In addition, serial ADAMTS13 measurements were not routinely available to correlate biochemical recovery with clinical response. Despite these limitations, the consistent and rapid responses observed after vincristine initiation in a highly refractory population support a meaningful therapeutic effect.

In conclusion, our findings suggest that vincristine is an effective and well-tolerated salvage therapy for refractory TTP, particularly in patients who fail to respond to rituximab. Vincristine continues to represent a valuable component of the therapeutic armamentarium for severe TTP, and further prospective, multi-center studies are warranted to define its optimal timing and comparative role alongside emerging therapies.

CONCLUSION

TTP remains a life-threatening condition requiring prompt and aggressive therapy. Although most patients achieve remission with plasma exchange and corticosteroids, a substantial subset develops refractory disease. In this single-center study, vincristine was appeared to be effective as third-line salvage therapy, inducing remission in more than 80% of patients who failed both plasma exchange and rituximab, and was associated with an overall survival rate of 92%. Vincristine was well tolerated, with no serious treatment-limiting toxicities observed.

These findings support vincristine as a valuable rescue therapy for refractory TTP, particularly in settings where access to newer agents may be limited. Prospective, multi-center studies are needed to better define the optimal timing of vincristine and its comparative role alongside emerging therapies in the management of refractory TTP.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Dicle University Ethics Committee for Non-interventional Clinical Researches (Date: 26.11.2025, Decision No: 74).

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: VD, AK, MOA; Design: VD, AK, MOA; Data Collection and/or Processing: VD, AK, MOA; Analysis and/or Interpretation: VD, AK, MOA; Literature Review: VD, AK, MOA; Writing the Article: VD; Critical Review: VD, AK, MOA.

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Impact of immunoglobulin subtype on the frequency and severity of renal failure in multiple myeloma: a real-world retrospective study

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Cite this article: Odabaşı Giden A. Impact of immunoglobulin subtype on the frequency and severity of renal failure in multiple myeloma: a real-world retrospective study. *J Curr Hematol Oncol Res.* 2026;4(2):57-62. doi:10.51271/JCHOR-0083

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Received: 06/04/2026

Accepted: 13/05/2026

Published: 18/05/2026

ABSTRACT

Aims: The aim of this study was to evaluate the association between immunoglobulin subtypes and the development of renal failure in patients with multiple myeloma.

Methods: This retrospective cross-sectional observational study included 52 patients diagnosed with multiple myeloma between January 2020 and May 2025. Patients were classified according to immunoglobulin subtype (IgG, IgA, and light chain). Renal failure was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m² and/or the presence of acute kidney injury at diagnosis, according to KDIGO criteria. Clinical, laboratory, and treatment-related data were obtained from electronic medical records. Statistical analyses were performed using appropriate parametric and non-parametric tests.

Results: The mean age of the patients was 66.2±10 years, and 57.7% were male. Renal failure was observed in 13.5% of patients. A significant association was found between advanced disease stage and renal failure (p=0.006). Immunoglobulin subtype was also significantly associated with renal failure (p=0.04), with a higher incidence observed in patients with lambda light chain disease. No significant associations were found between renal failure and other clinical or laboratory parameters.

Conclusion: Immunoglobulin subtype, particularly light chain disease, is associated with the development of renal failure in multiple myeloma. These findings highlight the importance of disease biology in renal involvement and support early diagnosis and appropriate treatment strategies to improve renal outcomes.

Keywords: Plasma cell neoplasms, kidney impairment, free light chains, disease severity, prognosis

INTRODUCTION

Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by the production of monoclonal immunoglobulins or free light chains and accounts for approximately 1-2% of all cancers worldwide.¹ The disease predominantly affects older adults and is associated with a wide spectrum of clinical manifestations resulting from end-organ damage, including anemia, bone destruction, hypercalcemia, and renal impairment. Among these, renal involvement represents one of the most clinically significant complications, contributing substantially to morbidity, mortality, and healthcare burden.¹

Renal dysfunction in MM is a complex and multifactorial process involving both monoclonal protein-mediated and non-myeloma-related mechanisms. Symptomatic MM is frequently associated with acute kidney injury (AKI), which may arise through several pathophysiological pathways.² The most common mechanism is light chain cast nephropathy, in which excessive free light chains (FLCs) are filtered through the glomerulus and precipitate within distal tubules, leading to tubular obstruction, inflammation, and progressive interstitial fibrosis.² Other monoclonal protein-related

conditions, such as light chain deposition disease and AL amyloidosis, may also contribute to renal damage.²

The pathogenic role of FLCs extends beyond tubular obstruction, as these proteins exert direct cytotoxic effects on tubular epithelial cells, induce oxidative stress, and activate pro-inflammatory and profibrotic signaling pathways.³ As a result, patients with light-chain-restricted MM are at particularly high risk for developing renal impairment, and early reduction of circulating FLC levels has been shown to be critical for renal recovery.⁴ In addition, several non-immunoglobulin-related factors, including dehydration, hypercalcemia, infections, nephrotoxic medications, and pre-existing chronic kidney disease, may further exacerbate renal dysfunction.²

Among the myeloma-defining events (hypercalcemia, renal impairment, anemia, and bone lesions), renal impairment has consistently been identified as a major determinant of survival outcomes.^{5,6} The prevalence of renal dysfunction at diagnosis varies depending on the criteria used, with reported rates ranging from 10% to 30%.^{2,7}

Importantly, MM exhibits marked biological heterogeneity, and differences in clinical presentation and organ involvement may be observed across immunoglobulin subtypes. Several studies have reported that light-chain-restricted MM is associated with a higher incidence of renal impairment compared with IgG and IgA subtypes. For example, renal dysfunction has been reported in approximately 55% of patients with light-chain disease, compared with 30% in IgG and 14% in IgA MM.⁸

In addition, recent regional and retrospective cohort analyses have further emphasized the prognostic relevance of ISS staging and renal dysfunction in MM, highlighting their combined impact on survival outcomes.⁹ These findings suggest that both disease burden and immunoglobulin subtype may contribute to renal involvement.

Despite these observations, direct comparative studies systematically evaluating the relationship between immunoglobulin subtype and both the frequency and severity of renal failure remain limited. Furthermore, the impact of these differences in the context of modern treatment strategies has not been fully elucidated. Therefore, this study aimed to systematically evaluate the association between immunoglobulin subtype and both the frequency and severity of renal failure in patients with MM in a real-world clinical setting in the era of modern therapeutic strategies.

METHODS

Ethics

The study was approved by the Ordu University Clinical Researches Ethics Committee (Date: 11.03.2026, Decision No: 2026/83). Due to the retrospective nature of the study, the requirement for informed consent was waived. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Setting

This retrospective, cross-sectional, observational cohort study was conducted at the Hematology Department of Ordu State Hospital and included patients diagnosed with MM between January 2020 and May 2025. The study was designed to evaluate the relationship between immunoglobulin subtype and renal failure at the time of diagnosis.

Study Population

The diagnosis of MM was established according to the International Myeloma Working Group (IMWG) criteria. Patients aged ≥ 18 years with a confirmed diagnosis of MM, documented immunoglobulin subtype (IgG, IgA, or light-chain), and available baseline renal function data were included.

Exclusion Criteria

Patients were excluded if they had:

- Advanced chronic kidney disease prior to MM diagnosis
- Primary renal disease unrelated to MM
- Incomplete clinical or laboratory data

- IgM MM (to avoid overlap with Waldenström macroglobulinemia)

Patient Classification

Patients were stratified into three groups according to immunoglobulin subtype:

- IgG MM
- IgA MM
- Light-chain-restricted MM

Data Collection

Clinical and laboratory data were retrospectively extracted from electronic medical records. Variables included demographic characteristics (age, sex), disease-related parameters (ISS stage, cytogenetic risk), laboratory values (creatinine, eGFR [calculated using the CKD-EPI equation], $\beta 2$ -microglobulin, hemoglobin, calcium), and treatment-related variables (regimen type, autologous stem cell transplantation [ASCT], maintenance therapy, and treatment response). Renal outcomes included the presence of AKI, renal failure at diagnosis, and dialysis requirement.

Definitions

Renal failure was defined as an eGFR < 60 ml/min/1.73 m² and/or the presence of AKI at diagnosis. AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The severity of renal impairment was assessed based on serum creatinine levels, eGFR values, and the requirement for renal replacement therapy. A history of dialysis included both prior and MM-related dialysis requirements. Due to the retrospective nature of the study, differentiation between AKI and pre-existing chronic kidney disease could not be consistently established for all patients.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 23.0.3 (MedCalc Software Ltd., Ostend, Belgium). Continuous variables were presented as mean \pm standard deviation (SD) or median (interquartile range, IQR) according to data distribution, while categorical variables were expressed as frequencies and percentages. Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. For comparisons between two independent groups, Student's t-test was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. For comparisons among three groups (ISS stages), one-way ANOVA or the Kruskal-Wallis H test was applied as appropriate. Post-hoc pairwise comparisons were performed using Tukey's test when ANOVA indicated statistical significance. Associations between categorical variables were evaluated using the chi-square test or Fisher's exact test when expected cell counts were < 5 . In multi-category comparisons with significant overall results, pairwise differences between proportions were assessed using the z-test for two proportions. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Due to the limited number of renal failure events, multivariable analysis was not performed to avoid overfitting and unreliable estimates. In addition, given the cross-

sectional design of the study, the analysis was primarily focused on identifying associations at the time of diagnosis rather than establishing independent predictors.

RESULTS

Patient Characteristics

A total of 52 patients with MM were included. The mean age was 66.2±10 years (range: 42-85), and 57.7% (n=30) were male. Renal failure was observed in 13.5% (n=7) of patients, while 86.5% (n=45) had no renal impairment. Bone disease was present in 82.7% (n=43) of patients.

A history of dialysis was noted in 15.4% (n=8) of patients, reflecting both prior and MM-related dialysis exposure. Renal failure was assessed at the time of diagnosis. Due to limitations inherent to the retrospective design, the exact timing of dialysis initiation (pre-diagnosis vs post-diagnosis) could not be clearly determined in all patients.

According to the ISS staging system, 51.9% (n=27) were stage I, 25% (n=13) stage II, and 23.1% (n=12) stage III.

The most common myeloma subtype was IgG (51.9%, n=27), followed by IgA (21.2%, n=11), kappa light chain (13.5%, n=7), and lambda light chain (13.5%, n=7).

Treatment regimens consisted predominantly of VCD (67.3%, n=35), followed by VRD (28.8%, n=15), while DRD and other regimens were each used in 1.9% (n=1). ASCT was performed in 59.6% (n=31) of patients.

Cytogenetic risk was standard in 82.7% (n=43) and high-risk in 17.3% (n=9). Nearly all patients received triplet therapy (98.1%, n=51). Maintenance therapy was administered in 26.9% (n=14), most commonly with lenalidomide (64.3%, n=9).

Treatment responses were predominantly favorable, with very good partial response (VGPR) achieved in 61.5% (n=32) and complete response (CR) in 17.3% (n=9). Progressive disease (PD), partial response (PR), and stable disease (SD) were observed in 13.5% (n=7), 3.8% (n=2), and 3.8% (n=2), respectively.

Following ASCT, 57.7% (n=30) of patients received maintenance therapy. Disease progression occurred in 55.8% (n=29), while 44.2% remained progression-free at last follow-up. At last follow-up, 76.9% (n=40) were alive. Mean follow-up was 44.8±36.5 months, and median PFS was 29.4±25.2 months (Table 1).

Laboratory Parameters

Mean albumin was 3.87±0.56 g/dl, mean CRP 10.16±14.96 mg/L, creatinine 1.18±1.26 mg/dl, and platelet count 206.8±76.4×10⁹/L. Mean β₂-microglobulin was 6.28±9.56 mg/L. Hemoglobin was 10.82±2.10 g/dl and eGFR 82.18±29.92 ml/min/1.73 m² (Table 2).

Renal Failure Analysis

Renal failure was not associated with age, sex, or bone disease (all p>0.05). Advanced ISS stages were significantly associated with renal failure (p=0.006).

Myeloma subtype was also significantly associated with renal failure (p=0.04), driven by increased incidence in lambda light-chain patients (p=0.02) and decreased incidence in IgG patients (p=0.03).

Albumin, CRP, platelet, and calcium levels were not associated with the development of renal failure. No significant associations were observed between renal failure and treatment-related variables or clinical outcomes (all p>0.05).

ISS Stage Analysis

ASCT and maintenance therapy were significantly more frequent in stage I patients (p=0.004 and p=0.01, respectively).

However, progression and survival outcomes did not differ significantly across ISS stages (all p>0.05), despite differences in treatment intensity (Table 3).

DISCUSSION

In this retrospective cohort of patients with MM, we systematically evaluated the relationship between immunoglobulin subtype and renal failure, while also identifying clinical and laboratory predictors associated with renal dysfunction. Our findings provide additional real-world evidence supporting the central role of disease biology—particularly immunoglobulin subtype and tumor burden—in the development of renal impairment.

The incidence of renal failure in our cohort was 13.5%, which is lower than the rates of 20-30% commonly reported in earlier studies.^{2,7} This difference is likely attributable to improvements in early diagnosis, supportive care strategies, and the widespread incorporation of novel therapeutic agents into frontline treatment. Recent studies suggest that early initiation of effective anti-myeloma therapy, particularly proteasome inhibitor-based regimens, may significantly reduce the severity of renal impairment at diagnosis and improve renal recovery rates.⁹

A key finding of this study is the significant association between immunoglobulin subtype and renal failure, particularly the increased risk observed in patients with lambda light-chain disease. This observation is consistent with previous reports demonstrating that light-chain-restricted MM is associated with a higher incidence of renal involvement compared with IgG or IgA subtypes.⁸ The pathogenic role of FLCs in renal injury is well established, as excessive production and filtration of monoclonal light chains result in tubular precipitation, obstruction, and subsequent inflammatory and fibrotic responses.^{10,11}

In addition to immunoglobulin subtype, several laboratory parameters were associated with renal failure. Patients with renal impairment had higher serum creatinine and β₂-microglobulin levels, along with lower hemoglobin and eGFR values. Elevated β₂-microglobulin is a well-recognized marker reflecting both tumor burden and renal dysfunction, and its association with renal failure in our cohort is consistent with previous studies.¹²

Table 1. Demographic and clinical characteristics according to renal failure

Characteristic	Total (n=52)	Renal failure absent (n=45)	Renal failure present (n=7)	p-value
Age, mean±SD (years)	66.2±10	65.9±9.5	67.8±10.5	0.65
Male sex, n (%)	30 (57.7)	25 (55.6)	5 (71.4)	0.69
Bone disease, n (%)	43 (82.7)	36 (80.0)	7 (100.0)	0.33
Dialysis history, n (%)	8 (15.4)	4 (8.9)	4 (57.1)	0.007
ISS stage, n (%)				0.006
• Stage I	27 (51.9)	26 (57.8)	1 (14.3)	
• Stage II	13 (25.0)	12 (26.7)	1 (14.3)	
• Stage III	12 (23.1)	7 (15.6)	5 (71.4)	
Myeloma subtype, n (%)				0.04
• IgG	27 (51.9)	26 (57.8)	1 (14.3)	
• IgA	11 (21.2)	9 (20.0)	2 (28.6)	
• Kappa light chain	7 (13.5)	6 (13.3)	1 (14.3)	
• Lambda light chain	7 (13.5)	4 (8.9)	3 (42.9)	
Treatment regimen, n (%)				>0.05
• VCD	35 (67.3)	31 (68.9)	4 (57.1)	
• VRD	15 (28.8)	13 (28.9)	2 (28.6)	
• DRD	1 (1.9)	1 (2.2)	0 (0.0)	
• Other	1 (1.9)	0 (0.0)	1 (14.3)	
Autologous stem cell transplantation, n (%)	31 (59.6)	27 (60.0)	4 (57.1)	>0.05
Cytogenetic risk, n (%)				>0.05
• Standard	43 (82.7)	37 (82.2)	6 (85.7)	
• High	9 (17.3)	8 (17.8)	1 (14.3)	
Maintenance therapy, n (%)	14 (26.9)	12 (26.7)	2 (28.6)	>0.05
Treatment response, n (%)				0.15
• CR	9 (17.3)	8 (17.8)	1 (14.3)	
• VGPR	32 (61.5)	27 (60.0)	5 (71.4)	
• PR	2 (3.8)	2 (4.4)	0 (0.0)	
• SD	2 (3.8)	2 (4.4)	0 (0.0)	
• PD	7 (13.5)	6 (13.3)	1 (14.3)	
Progression, n (%)	29 (55.8)	26 (57.8)	3 (42.9)	0.69
Alive at last follow-up, n (%)	40 (76.9)	36 (80.0)	4 (57.1)	0.33

Data are presented as mean±SD or n (%). p-values were calculated using Student's t-test, Mann-Whitney U test, Chi-square test, or Fisher's exact test, as appropriate. ISS: International Staging System, CR: Complete response, VGPR: Very good partial response, PR: Partial response, SD: Stable disease, PD: Progressive disease, VCD: Bortezomib-cyclophosphamide-dexamethasone, VRD: Bortezomib-lenalidomide-dexamethasone, DRD: Daratumumab-lenalidomide-dexamethasone

Table 2. Laboratory parameters according to renal failure

Parameter	Total (n=52)	Renal failure absent (n=45)	Renal failure present (n=7)	p-value
Albumin (g/dl), mean±SD	3.87±0.56	3.84±0.52	4.05±0.79	0.38
CRP (mg/L), median (IQR)	3.9 (2-10.5)	3.7 (2-9.75)	2.2 (1.1-22.36)	0.46
Creatinine (mg/dl), median (IQR)	0.88 (0.60-1.25)	0.80 (0.55-0.95)	3.15 (1.39-6.00)	<0.001
Platelets (×10 ⁹ /L), median (IQR)	192 (150-270)	186 (150-266.5)	180 (94-286)	0.46
β2-microglobulin (mg/L), median (IQR)	3.6 (2.4-5.9)	3.4 (2.41-3.6)	22.2 (9.8-42)	<0.001
Calcium (mg/dl), mean±SD	8.92±0.69	8.86±0.68	9.35±0.68	0.08
Hemoglobin (g/dl), mean±SD	10.82±2.10	11.09±2.04	9.10±1.77	0.02
eGFR (ml/min/1.73 m ²), mean±SD	82.18±29.92	91.03±18.51	25.29±9.82	<0.001

SD: Standard deviation, CRP: C-reactive protein, IQR: Interquartile range eGFR: Estimated glomerular filtration rate. Data are presented as mean±SD or median (IQR). p-values were calculated using Student's t-test or Mann-Whitney U test, as appropriate.

Importantly, renal impairment has historically been considered an adverse prognostic factor in MM.¹³ The pathophysiology of renal impairment is predominantly driven by light chain-mediated injury, particularly cast nephropathy, which remains the most common mechanism of kidney damage.^{14,15}

We also observed a significant association between advanced ISS stage and renal failure. Patients with more advanced disease stages were more likely to develop renal impairment, supporting previous findings that renal dysfunction is more frequent in aggressive disease phenotypes.^{5,6} However, survival outcomes did not differ significantly across ISS

Table 3. Clinical characteristics, treatment, and outcomes by ISS stage

Characteristic	Stage I (n=27)	Stage II (n=13)	Stage III (n=12)	p-value
Age, mean±SD (years)	65.7±6.1	69.8±10.9	63.5±11.1	0.28
Male sex, n (%)	15 (55.6)	7 (53.8)	8 (66.7)	0.77
Bone disease, n (%)	22 (81.5)	10 (76.9)	11 (91.7)	0.21
Dialysis history, n (%)	3 (11.1)	3 (23.1)	2 (16.7)	0.47
Myeloma subtype, n (%)				0.60
• IgG	15 (55.6)	6 (46.2)	6 (50.0)	
• IgA	6 (22.2)	3 (23.1)	2 (16.7)	
• Kappa	3 (11.1)	2 (15.4)	2 (16.7)	
• Lambda	3 (11.1)	2 (15.4)	2 (16.7)	
Autologous stem cell transplantation, n (%)	22 (81.5)	5 (38.5)	4 (33.3)	0.004
Maintenance therapy after ASCT, n (%)	21 (77.8)	5 (38.5)	4 (33.3)	0.01
Disease progression, n (%)	16 (59.3)	6 (46.2)	7 (58.3)	0.76
Alive at last follow-up, n (%)	22 (81.5)	9 (69.2)	9 (75.0)	0.69

SD: Standard deviation, ISS: International Staging System, ASCT: Autologous stem cell transplantation. Data are presented as mean±SD or n (%). p-values were calculated using one-way ANOVA, Kruskal-Wallis test, chi-square test, or Fisher's exact test, as appropriate.

stages in our cohort. This finding contrasts with the broader literature and may be attributable to the relatively small sample size and retrospective design.¹⁶

Despite the increasing interest in extracorporeal strategies for removing circulating FLCs, such as high-cutoff hemodialysis, their clinical benefit remains uncertain.¹⁷

Limitations

This study has several limitations that should be acknowledged. First, the retrospective and cross-sectional design may introduce selection bias and limit the ability to establish causal relationships; therefore, the findings should be interpreted as associations rather than causative effects.

Second, the study was conducted at a single center, which may restrict the generalizability of the findings to broader populations. Third, the relatively small sample size (n=52) and the limited number of renal failure events (n=7) may have reduced the statistical power and limited the ability to perform multivariable analyses. Performing regression modeling under these conditions could lead to overfitting and unreliable estimates.

Additionally, serum FLC measurements and FLC ratio were not consistently available due to the retrospective nature of the study, which represents an important limitation given their central role in the pathophysiology of renal involvement.

Furthermore, differentiation between AKI and pre-existing chronic kidney disease, as well as the exact timing of dialysis initiation, could not be consistently determined for all patients. Finally, longitudinal renal outcomes and dynamic changes in renal function during follow-up were not systematically evaluated.

Future prospective, multicenter studies with larger patient populations and comprehensive statistical analyses are needed to validate these findings and further clarify the relationship between immunoglobulin subtypes and renal involvement in MM.

CONCLUSION

As a result, immunoglobulin subtype appears to be associated with the development of renal failure in patients with MM, with a particularly higher risk observed in those with lambda light-chain disease. Advanced disease stage was also significantly associated with renal impairment. These findings highlight the importance of disease biology in renal involvement and underscore the need for early recognition and appropriate treatment strategies to improve renal outcomes. Further large-scale prospective studies are warranted to confirm these results and to better define the prognostic impact of immunoglobulin subtypes in MM.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Ordu University Clinical Researches Ethics Committee (Date: 11.03.2026, Decision No: 2026/83).

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 author declare no conflicts of interest related to this study.

Financial Disclosure

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

Author Contributions

The author is solely responsible for the entirety of conception, execution, analysis, and writing of the manuscript.

Acknowledgments

The authors would like to thank all healthcare professionals involved in the diagnosis, treatment, and follow-up of the patients included in this study.

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Prognostic value of the PLACE score in a Turkish cohort of metastatic pleural mesothelioma

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Cite this article: Çıtakkul İ, Bakkal Temi Y, Zengin H, et al. Prognostic value of the PLACE score in a Turkish cohort of metastatic pleural mesothelioma. *J Curr Hematol Oncol Res.* 2026;4(2):63-69. doi:10.51271/JCHOR-0084

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Received: 19/04/2026

Accepted: 13/05/2026

Published: 18/05/2026

ABSTRACT

Aims: Pleural mesothelioma is an aggressive malignancy with poor prognosis and limited therapeutic options. Reliable prognostic models are essential for risk stratification and clinical decision-making. The recently developed PLACE score has shown promising results in Chinese populations; however, its generalizability remains uncertain. This study aimed to externally validate the PLACE prognostic score in a Turkish cohort of patients with metastatic epithelioid pleural mesothelioma.

Methods: This retrospective cohort study included patients diagnosed with metastatic epithelioid pleural mesothelioma at a single tertiary center between January 2016 and September 2025. Clinical and laboratory data at diagnosis were collected, and the PLACE score was calculated for each patient. Overall survival (OS) was analyzed using the Kaplan–Meier method, and differences between risk groups were compared using the log-rank test. Cox proportional hazards regression analysis was performed to evaluate the association between prognostic variables and survival. The discriminative ability of the PLACE score was assessed using receiver operating characteristic (ROC) curve analysis.

Results: A total of 48 patients were included, with a median age of 66 years. According to the PLACE score, 33.3% of patients were classified as low-risk and 66.7% as high-risk. The median OS was 21.06 months. Patients in the low-risk group had significantly longer survival compared to the high-risk group (37.98 vs. 15.6 months, $p=0.033$). Time-dependent ROC analysis demonstrated increasing discriminative ability over time, with AUC values ranging from 0.554 at 6 months to 0.717 at 24 months. In Cox regression analysis, high-risk patients had a significantly increased risk of mortality (HR: 2.28, 95% CI: 1.04–4.95, $p=0.037$). In multivariable analysis, the PLACE risk group remained significantly associated with OS.

Conclusion: The PLACE score retains prognostic significance in Turkish patients with metastatic pleural mesothelioma but demonstrates reduced discriminative performance compared to the original study. These findings emphasize the need for external validation and potential population-specific recalibration of prognostic models.

Keywords: Mesothelioma, PLACE score, prognostic score, survival

INTRODUCTION

Pleural mesothelioma is a rare but aggressive malignancy primarily associated with asbestos exposure, characterized by poor prognosis and limited therapeutic options.^{1,2} The median survival typically ranges from 12 to 18 months from diagnosis, making accurate prognostic assessment crucial for clinical decision-making, treatment planning, and patient counseling.^{3,4} The heterogeneous nature of the disease and variable patient outcomes underscore the need for reliable prognostic tools that can stratify patients into meaningful risk categories.

Türkiye is recognized as one of the endemic regions for malignant pleural mesothelioma, primarily due to environmental asbestos exposure, particularly in certain rural areas where asbestos-containing soil has been traditionally

utilized for domestic purposes.⁵⁻⁷ Previous epidemiological studies have indicated a higher incidence of mesothelioma in regions such as Central Anatolia and Southeastern Türkiye, where environmental exposure, rather than occupational exposure, predominates.⁸ This distinctive exposure pattern differentiates Türkiye from many Western countries and highlights the necessity of evaluating prognostic models within this specific population. Consequently, the validation of prognostic scoring systems in Turkish cohorts is crucial to ensure their clinical applicability and reliability in real-world settings.

All patients received first-line systemic therapy consisting of pemetrexed, cisplatin, and bevacizumab.^{9,10} Immunotherapy-based combination regimens were not included, as these

treatments were not reimbursed in our national healthcare system for an extended period and only became available more recently.¹¹⁻¹³

Several prognostic scoring systems have been developed for pleural mesothelioma, including the CALGB (Cancer and Leukemia Group B) score, EORTC (European Organisation for Research and Treatment of Cancer) score, and more recently, the LENT and BRIMS scores.^{4,14-16} However, these models have shown variable performance across different populations and healthcare settings, highlighting the challenges in developing universally applicable prognostic tools for this complex malignancy.

Recently, Zhang and colleagues¹⁷ developed the PLACE prognostic score specifically for patients with pleural mesothelioma. The PLACE score incorporates five readily available clinical and laboratory parameters: platelet count (PLT) $>289.5 \times 10^9/L$ (+1 point), lymphocyte count $>1.785 \times 10^9/L$ (-1 point), age >73 years (+1 point), calcium >2.145 mmol/L (-1 point), and Eastern Cooperative Oncology Group performance status (ECOG PS) >2 (+2 points).¹⁷ Patients are classified as low-risk (score <0) or high-risk (score 0-3) based on the total score.¹⁷

In the original development study, the PLACE score demonstrated excellent discriminative ability with an area under the curve (AUC) of 0.900 at 6 months in the development cohort (n=95) and 0.761 in the validation cohort (n=23).¹⁷ High-risk patients showed significantly worse survival compared to low-risk patients, with hazard ratios of 3.878 and 3.574 in the development and validation cohorts, respectively.¹⁷ However, the original study was conducted exclusively in Chinese patients at two hospital centers in Beijing, and the authors acknowledged that “the proposed model can only be applied to patients of Chinese ethnicity now and not currently generalizable to the overall global population”.¹⁷

The generalizability of prognostic models across different populations, healthcare systems, and geographic regions is a critical consideration for clinical implementation. Ethnic, genetic, environmental, and healthcare delivery differences can significantly impact model performance, necessitating external validation studies in diverse populations. The original PLACE score developers emphasized the need for “multi-centre and large sample studies worldwide” to establish broader applicability.¹⁷

Given the promising initial results of the PLACE score and the recognized need for validation in non-Chinese populations, we conducted this study to evaluate the prognostic performance of the PLACE score in a Turkish cohort. Our objectives were to: (1) assess the discriminative ability of the PLACE score in our cohort, (2) evaluate the survival differences between PLACE-defined risk groups, and (3) determine the clinical utility of this scoring system in our patient population. This validation study aims to contribute to the growing evidence base for prognostic tools in pleural mesothelioma and inform clinical decision-making across diverse healthcare settings.

METHODS

Ethics

The study was initiated after obtaining an approval from Kocaeli University Ethics Committee for Non-interventional Clinical Researches (Date: 09.04.2026, Decision No: 2026/99). The study was conducted in accordance with the Declaration of Helsinki.

Study Design and Population

This retrospective cohort study was conducted at Kocaeli University Medical Center to validate the prognostic performance of the PLACE score in patients with pleural mesothelioma. We reviewed electronic medical records of patients diagnosed with pleural mesothelioma between January 2016 and September 2025.

Patient Selection

Inclusion criteria were: (1) histologically confirmed pleural mesothelioma with epithelioid subtype, (2) de novo metastatic disease at presentation, (3) age ≥ 18 years, (4) treatment with first-line pemetrexed, cisplatin, and bevacizumab combination therapy, and (5) availability of complete clinical and laboratory data required for PLACE score calculation. Exclusion criteria included: (1) non-epithelioid histological subtypes, (2) locally advanced disease without distant metastases, (3) previous treatment for mesothelioma, (4) incomplete medical records, and (5) loss to follow-up within 30 days of diagnosis.

A total of 48 patients met the inclusion criteria and were included in the final analysis.

Data Collection

Clinical and laboratory data were extracted from electronic medical records at the time of diagnosis, prior to initiation of systemic therapy. The following variables were collected: demographic characteristics (age, gender), Eastern Cooperative Oncology Group performance status (ECOG PS), sites of metastatic disease, and laboratory parameters including complete blood count (platelet count, lymphocyte count), serum chemistry panel (calcium, albumin), and other relevant biomarkers.

PLACE Score Calculation

The PLACE score was calculated for each patient using the original scoring system developed by Zhang et al.¹⁷ The score incorporates five parameters: platelet count $>289.5 \times 10^9/L$ (+1 point), lymphocyte count $>1.785 \times 10^9/L$ (-1 point), age >73 years (+1 point), serum calcium >2.145 mmol/L (-1 point), and ECOG performance status >2 (+2 points). The total score was calculated by summing individual component scores, and patients were classified into risk groups according to the original criteria: low-risk (total score <0) and high-risk (total score 0-3).¹⁷

Treatment Protocol

All patients received first-line systemic therapy consisting of pemetrexed (500 mg/m²), cisplatin (75 mg/m²), and bevacizumab (15 mg/kg) administered intravenously every 21 days.^{9,10} Treatment continued until disease progression,

unacceptable toxicity, or patient withdrawal of consent. Standard premedication with folic acid and vitamin B12 supplementation was provided according to institutional protocols.⁹

Follow-up and Outcome Assessment

Patients were followed from the date of diagnosis until death, loss to follow-up, or the end of the study period. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Progression-free survival (PFS) was defined as the time from treatment initiation to radiological or clinical disease progression or death, whichever occurred first. Survival status was determined through medical record review, hospital databases, and when necessary, contact with patients or family members.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as median with interquartile range (IQR) or mean with standard deviation, as appropriate. Survival curves were constructed using the Kaplan-Meier method, and differences between risk groups were compared using the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards regression analysis. The multivariable model included two covariates, yielding an events-per-variable (EPV) ratio of 17.0, which satisfies the recommended minimum threshold of ≥ 10 . The discriminative ability of the PLACE score was assessed using time-dependent ROC analysis. An incident/dynamic definition was applied: cases were defined as patients experiencing the event (death) before a predefined time point *t*, and controls were patients alive at time *t*. AUC values were calculated at 6, 12, 18, and 24 months. For comparison with the original PLACE study, a binary ROC analysis based on OS status (alive vs. deceased) was also performed as a supplementary analysis. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics for Windows version 29.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 48 patients participated in the study. The median age was 66 years (IQR: 59.8–71.0), with 66.7% (n=32) being male and 33.3% (n=16) female. Regarding smoking status, 54.2% (n=26) of patients were smokers and 45.8% (n=22) were non-smokers. The ECOG performance status was 0-1 in 85.4% (n=41) of patients and ≥ 2 in 14.6% (n=7). Regarding comorbidities, diabetes mellitus was present in 22.9% (n=11), hypertension in 56.3% (n=27), COPD in 20.8% (n=10), and coronary artery disease in 31.3% (n=15). According to the PLACE risk classification, 33.3% (n=16) of patients were categorized as low-risk, while 66.7% (n=32) were classified as high-risk. Laboratory parameters were reported as median (IQR). Urea was 33.5 (26.9-40.3) mg/dl, creatinine 0.80 (0.668-0.915) mg/dl, and GFR 90.0 (82.7-100.0) ml/min/1.73 m². Albumin was 38.0 (34.7-40.0) g/L, calcium 2.11 (2.03-2.18) mmol/L, AST 17.0 (12.8-28.0) U/L, ALT 14.2 (10.9-23.3) U/L, and LDH 164 (130-213) U/L. Inflammatory and hematological parameters included CRP 28.8 (6.4-46.5) mg/L, WBC 7870

(6528-9665) $\times 10^3/\mu\text{L}$, neutrophils 5380 (3668-6795) $\times 10^3/\mu\text{L}$, hemoglobin 12.5 (11.2-13.6) g/dl, lymphocytes 1700 (1380-2100) $\times 10^3/\mu\text{L}$, and platelets 304 (252-428) $\times 10^3/\mu\text{L}$. **Table 1** presents the clinical and demographic characteristics of the study population. (n=48).

Table 1. Baseline characteristics of the study population (n=48)

Variable	Value n (%) or median (IQR)
Age, years (median, IQR)	66 (59.8-71.0)
Sex (male/female)	32 (66.7%)/16 (33.3%)
Smoking status (yes/no)	26 (54.2%)/22 (45.8%)
ECOG performance status	
0-1	41 (85.4%)
≥ 2	7 (14.6%)
Comorbidities	
Diabetes mellitus	11 (22.9%)
Hypertension	27 (56.3%)
COPD	10 (20.8%)
Coronary artery disease	15 (31.3%)
Sites of metastasis	
Lung metastasis (yes/no)	21 (43.8%)/27 (56.2%)
Liver metastasis (yes/no)	4 (8.3%)/44 (91.7%)
Bone metastasis (yes/no)	8 (16.7%)/40 (83.3%)
Brain metastasis (yes/no)	3 (6.3%)/45 (93.7%)
Mediastinal lymph node metastasis (yes/no)	27 (56.3%)/21 (43.7%)
PLACE risk group	
Low risk	16 (33.3%)
High risk	32 (66.7%)
Laboratory parameters (Median, IQR)	
Urea (mg/dl)	33.5 (26.9-40.3)
Serum creatinine (mg/dl)	0.80 (0.668-0.915)
GFR (ml/min/1.73 m ²)	90.0 (82.7-100.0)
Albumin (g/L)	38.0 (34.7-40.0)
Calcium (mmol/L)	2.11 (2.03-2.18)
AST (U/L)	17.0 (12.8-28.0)
ALT (U/L)	14.2 (10.9-23.3)
LDH (U/L)	164 (130-213)
CRP (mg/L)	28.8 (6.4-46.5)
WBC ($\times 10^3/\mu\text{L}$)	7870 (6528-9665)
Neutrophils ($\times 10^3/\mu\text{L}$)	5380 (3668-6795)
Hemoglobin (g/dl)	12.5 (11.2-13.6)
Lymphocytes ($\times 10^3/\mu\text{L}$)	1700 (1380-2100)
Platelets ($\times 10^3/\mu\text{L}$)	304 (252-428)

ECOG: Eastern Cooperative Oncology Group, COPD: Chronic obstructive pulmonary disease, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cell count, IQR: Interquartile range

Time-dependent ROC analysis demonstrated increasing discriminative ability over time, with AUC values of 0.554 (95% CI: 0.378–0.707) at 6 months, 0.576 (95% CI: 0.440–0.712) at 12 months, 0.669 (95% CI: 0.541–0.785) at 18 months, and 0.717 (95% CI: 0.572–0.844) at 24 months. For supplementary comparison with the original PLACE study, binary ROC analysis yielded an AUC of 0.617 (95% CI: 0.413–0.821) (**Figure 1**).

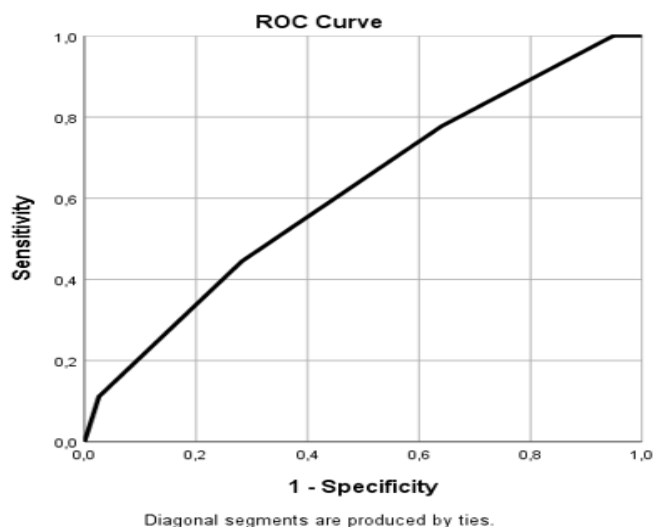


Figure 1. Receiver operating characteristic (ROC) curve of the PLACE score for predicting survival status (alive vs. deceased), shown for supplementary comparison with the original PLACE study. The area under the curve (AUC) was 0.617 (95% CI: 0.413–0.821). Primary discrimination analysis using time-dependent ROC is reported in the text.

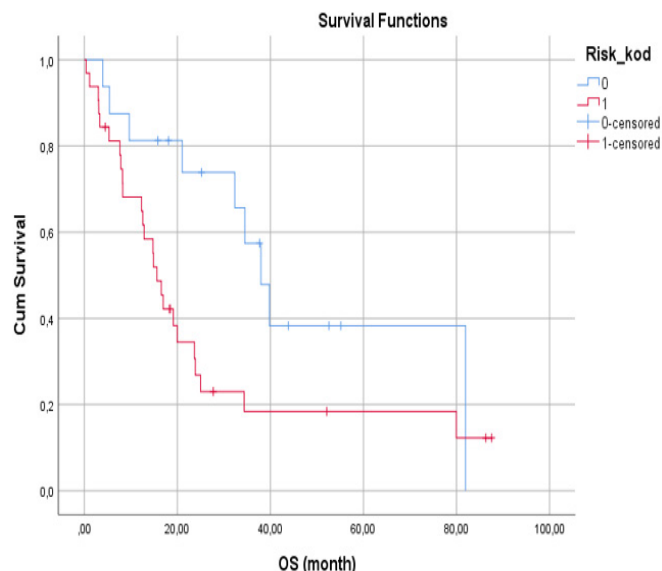


Figure 3. Kaplan–Meier survival curves according to PLACE risk groups. Patients in the low-risk group demonstrated significantly longer survival compared to the high-risk group (37.98 vs. 15.6 months, $p=0.033$).

The Kaplan–Meier survival curve for OS is shown in **Figure 2**, with a median OS of 21.06 months (95% CI: 12.99–29.13). The analysis of OS across different risk groups demonstrated a statistically significant difference. Patients in the low-risk group exhibited a longer median OS of 37.98 months (95% CI: 30.26–45.69), whereas those in the high-risk group had a shorter median OS of 15.6 months (95% CI: 12.62–18.59) ($p=0.033$). These findings are summarized in **Figure 3**.

levels (HR: 0.18, 95% CI: 0.08–0.39, $p<0.001$) and albumin levels (HR: 0.92, 95% CI: 0.86–0.98, $p=0.011$) were associated with enhanced survival outcomes. Variables such as age, sex, ECOG performance status, lung metastasis, mediastinal lymph node involvement, lymphocyte count, platelet count, hemoglobin, LDH, and CRP levels did not demonstrate a significant association with OS in the univariable analysis. Univariable Cox regression analysis results are summarized in **Table 2**.

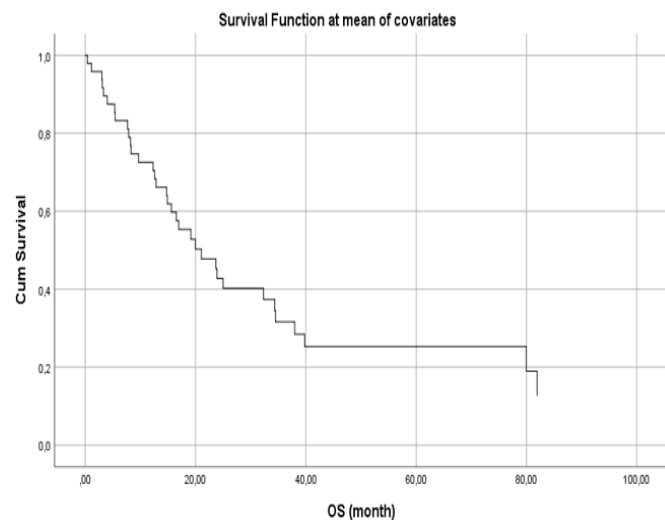


Figure 2. Kaplan–Meier survival curve for overall survival (OS). The median overall survival was 21.06 months (95% CI: 12.99–29.13).

During follow-up, 34 patients (70.8%) died, while 14 patients (29.2%) were alive at the time of analysis. Univariable Cox regression analysis revealed a significant association between the PLACE risk group and OS. Specifically, patients classified within the high-risk group exhibited a markedly elevated risk of mortality compared to those in the low-risk group (HR: 2.28, 95% CI: 1.04–4.95, $p=0.037$). Among the clinical variables examined, the presence of liver metastasis (HR: 2.21, 95% CI: 1.06–4.62, $p=0.035$), bone metastasis (HR: 3.00, 95% CI: 1.55–5.83, $p=0.001$), and brain metastasis (HR: 2.46, 95% CI: 1.14–5.32, $p=0.022$) were also significantly correlated with poorer OS outcomes. Conversely, elevated calcium

Variable	HR (95% CI)	p-value
PLACE risk group (high vs low)	2.28 (1.04–4.95)	0.037
Age (years)	1.01 (0.98–1.04)	0.495
Sex (male vs female)	1.16 (0.55–2.46)	0.692
ECOG performance status	1.14 (0.78–1.68)	0.502
Lung metastasis	1.78 (0.92–3.45)	0.087
Liver metastasis	2.21 (1.06–4.62)	0.035
Bone metastasis	3.00 (1.55–5.83)	0.001
Brain metastasis	2.46 (1.14–5.32)	0.022
Mediastinal lymph node metastasis	1.64 (0.86–3.13)	0.134
Calcium (mmol/L)	0.18 (0.08–0.39)	<0.001
HGB (g/dl)	1.09 (0.922–1.303)	0.518
Lymphocyte count ($\times 10^3/\mu\text{L}$)	1.00 (0.999–1.000)	0.518
Platelets ($\times 10^3/\mu\text{L}$)	1.00 (0.998–1.004)	0.477
Albumin (g/L)	0.92 (0.86–0.98)	0.011
LDH (U/L)	1.002 (0.999–1.005)	0.117
CRP (mg/L)	1.002 (0.994–1.01)	0.637

HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group performance status, HGB: Hemoglobin, LDH: Lactate dehydrogenase, CRP: C-reactive protein

Multivariable Cox regression analysis revealed that the PLACE risk group remained an independent predictor of OS, even after adjusting for serum albumin level (HR: 1.776, 95% CI: 1.192–2.648, $p=0.005$). In contrast, serum albumin level did not exhibit an independent association with OS (HR: 0.934, 95% CI: 0.868–1.005, $p=0.069$). The overall model was statistically significant ($p=0.001$).

DISCUSSION

This study constitutes the inaugural external validation of the PLACE prognostic score within a Turkish cohort and is among the limited investigations assessing its efficacy beyond the initial Chinese cohort. Our results indicate that, while the PLACE score maintains statistically significant prognostic utility in patients with metastatic epithelioid pleural mesothelioma, its discriminative capacity is considerably diminished in comparison to the original development study.

Performance Comparison with Original Study

In the original development study by Zhang et al.,¹⁷ the PLACE score demonstrated excellent discriminative ability with an AUC of 0.900 in the development cohort and 0.761 in the validation cohort. The HR for high-risk versus low-risk patients were 3.878 and 3.574, respectively.¹⁷ In contrast, our study demonstrated time-dependent AUC values ranging from 0.554 at 6 months to 0.717 at 24 months, with a hazard ratio of 2.28 (95% CI: 1.04–4.95, $p=0.037$). For supplementary comparison with the original study, binary ROC analysis yielded an AUC of 0.617 (95% CI: 0.413–0.821). While our results remain statistically significant, the reduced discriminative performance compared to the original Chinese cohort suggests important population-specific differences that may limit the universal applicability of the PLACE score. Notably, the time-dependent AUC improved over the follow-up period (0.717 at 24 months), suggesting that the score may have greater clinical value for longer-term prognostic stratification.

Population and Treatment Differences

Several factors may account for the diminished performance observed in our cohort. Firstly, the original PLACE score was specifically developed for Chinese patients, with the authors explicitly stating that “the proposed model can only be applied to patients of Chinese ethnicity now and not currently generalizable to the overall global population”.¹⁷ Ethnic variations in disease biology, genetic background, and baseline laboratory characteristics may contribute to the observed discrepancies in model performance across different populations.¹⁸

Although our results remained statistically significant, the reduced discriminative ability indicates that the model may not perform consistently across diverse populations. Furthermore, the use of a predefined threshold (score=0) for risk stratification, as established in the original study, may not be entirely optimal for our cohort and could have contributed to the observed reduction in performance. While we did not attempt to redefine alternative thresholds, our findings suggest that population-specific recalibration of risk stratification may warrant further investigation.

Secondly, our study population was more homogeneous, comprising only patients with de novo metastatic epithelioid disease treated with a uniform first-line regimen. In contrast, the original cohort included patients with stages I–III disease, with 92.6% receiving chemotherapy with or without anti-angiogenesis therapy.¹⁷ This heterogeneity in the development dataset may have contributed to the higher discriminative performance reported in the original study.

Clinical Implications

Although discriminative performance was limited, the PLACE score retained statistically significant prognostic stratification ability in our cohort. The significant survival difference between risk groups (37.98 months vs. 15.6 months, $p=0.033$) suggests that the score can still inform clinical decision-making and patient counseling. However, clinicians should be aware of the limitations when applying this score to non-Chinese populations or patients with metastatic disease.

The original authors emphasized that the PLACE score relies on “commonly monitored clinical and laboratory indicators” that do not add “additional physical and economic burden to the patient”.¹⁷ This practical advantage remains valid in our validation, as all components of the score are routinely available in clinical practice. The PLACE score may serve as a practical bedside tool for risk stratification in routine clinical practice.

Additional Prognostic Factors

Our analysis identified several additional prognostic factors not included in the original PLACE model, including specific metastatic sites (liver, bone, brain) and serum albumin levels.¹⁹ These findings suggest potential opportunities for model refinement or development of population-specific modifications to improve prognostic accuracy.

Limitations

Our study has several limitations that should be acknowledged. The relatively small sample size ($n=48$) limits the statistical power and generalizability of our findings. Given the rarity of pleural mesothelioma, our sample size is comparable to many single-center studies in the literature. The wide confidence interval of the AUC (0.413–0.821) reflects this limited sample size and should be interpreted with caution; however, this is consistent with the rarity of the disease and the sample sizes reported in similar validation studies, including the original PLACE validation cohort ($n=23$). Although the multivariable model achieved an adequate EPV ratio of 17.0, variable selection was not fully pre-specified, and the risk of overfitting cannot be entirely excluded in small datasets; this should be considered when interpreting the multivariable results. The retrospective design introduces potential selection bias, and the single-center nature may limit external validity. Additionally, our focus on metastatic epithelioid disease represents a subset of the broader pleural mesothelioma population, which may limit comparability with the original mixed-stage cohort.

The original study authors noted similar limitations, including “small sample sizes,” “short follow-up time in validation cohort,” and the need for “multi-centre and large sample studies worldwide”. Our study contributes to addressing these knowledge gaps but highlights the ongoing need for larger, multicenter validation studies.¹⁷

The absence of immunotherapy-based regimens reflects real-world practice in our country, where such treatments were not reimbursed for a prolonged period and only recently became accessible. This limitation should be considered when interpreting survival outcomes.

The reduced performance of the PLACE score in our population underscores the importance of external validation across diverse populations before widespread clinical implementation. Future research should focus on: (1) larger multicenter validation studies in non-Chinese populations, (2) investigation of population-specific modifications to improve model performance, (3) incorporation of additional prognostic variables such as molecular markers or imaging parameters, and (4) prospective validation studies to confirm clinical utility.

The original authors acknowledged that their model “lacks relevant genetic molecular variables and imaging variables”, suggesting opportunities for model enhancement. Integration of modern biomarkers, genomic data, and advanced imaging features may improve prognostic accuracy across diverse populations. Furthermore, asbestos exposure status was unknown in a substantial proportion of patients (85.4%), which may affect the generalizability of our findings; however, as asbestos exposure is not a component of the PLACE score, this does not affect the validity of the primary analyses.

CONCLUSION

This study provides the first external validation of the PLACE prognostic score in a non-Chinese population with metastatic epithelioid pleural mesothelioma. While the score maintains statistical significance for survival prediction, the reduced discriminative performance (time-dependent AUC ranging from 0.554 at 6 months to 0.717 at 24 months, compared to 0.900 in the original study) highlights important limitations in cross-population generalizability. The PLACE score retains clinical utility for risk stratification in our population, but clinicians should interpret results with caution when applying this tool to non-Chinese patients or those with metastatic disease.

Our findings emphasize the critical importance of external validation studies for prognostic models and support the original authors’ call for “multi-centre and large sample studies worldwide”. Future research should focus on larger validation studies, population-specific model modifications, and incorporation of additional prognostic variables to develop more universally applicable prognostic tools for pleural mesothelioma patients across diverse populations and healthcare settings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated after obtaining an approval from Kocaeli University Ethics Committee for Non-interventional Clinical Researches (Date: 09.04.2026, Decision No: 2026/99).

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: İÇ, YBT; Design: İÇ, YBT; Control: İÇ, YBT, KU, DÇ, UK; Resources: HZ, MÖ; Materials: İÇ, YBT; Data Collection and/or Processing: HZ, MÖ, İÇ, EB; Analysis and/or Interpretation: İÇ, YBT, KU, DÇ, UK; Literature Review: İÇ, YBT, EB; Writing the Article: İÇ, YBT, KU, DÇ, UK; Critical Review: İÇ, YBT, KU, DÇ, UK.

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Moya Moya syndrome in beta thalassemia major- silent puff, alarming crisis: a case and review of literature

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Cite this article: Gogoi RM, Chand S, Sood N, Goyal C, Goyal V. Moya Moya syndrome in beta thalassemia major- silent puff, alarming crisis: a case and review of literature. *J Curr Hematol Oncol Res.* 2026;4(2):70-73. doi:10.51271/JCHOR-0085

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Received: 04/01/2026

Accepted: 02/04/2026

Published: 18/05/2026

ABSTRACT

Our aim is to report a rare case of beta Thalassemia major with Moya Moya syndrome (MMS) presenting as acute ischemic stroke who was managed with encephaloduroarteriomyosynangiosis (EDAMS). MMS is an intracranial angiopathy with progressive stenosis of the distal portion of internal carotid artery (ICA) causing development of small collaterals traversing the basal ganglia and thalamus, giving “puff of smoke” appearance. MMS presents commonly as ischemic stroke in children and haemorrhagic stroke in adults. There are only few reported cases of MMS associated with Thalassemia. We obtained an informed consent form from the patient involved. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A 23-year-male with beta thalassemia major, diagnosed at 9 months of age on intermittent blood transfusion till the age of 22 years followed by chemotherapy (thalidomide 50 mg once daily). After chemotherapy he did not require transfusion. He presented with acute confusional and dysarthria for 10-12 days. On examination, he had mild pallor and hepatosplenomegaly. MRI Brain showed multiple acute infarcts in left parietal, left centrum semi ovale and corona radiata along with multifocal chronic infarcts. DSA showed Moya Moya like phenomenon, Suzuki grade IV. He was treated with single antiplatelet (acetyl salicylate 75 mg/day) and other supportive measures. Left sided (EDAMS) was done 1 month after stroke, which he tolerated well. We plan to re-introduce thalidomide on follow-up. MMS along with beta-thalassemia major is rare. Any neurological symptom indicating possible stroke warrants neuroimaging like MRI Brain and angiography of head-neck vessels in order to exclude MMS or other occlusive arteriopathy. Our case is unique as apart from MMS being rare in Thalassemia, very few such cases undergo surgical revascularization management.

Keywords: Moya Moya syndrome, Suzuki, beta thalassemia, transfusion, encephaloduroarteriomyosynangiosis, thalidomide

INTRODUCTION

Moya Moya syndrome (MMS) is an intracranial angiopathy in which there is progressive stenosis of the distal portion of the internal carotid artery (ICA), leading to development of small collaterals traversing the basal ganglia and thalamus, giving the characteristic “puff of smoke” appearance. Suzuki et al.¹ described six angiographic stages from stage 1, revealing a narrowing of the carotid forks to stage 6 in which the moyamoya vessels disappear and collateral circulation is produced solely from the external carotid arteries.¹ MMS presents commonly as ischemic stroke in children and haemorrhagic stroke in adults. Hypercoagulability followed by thromboembolic event is a known complication of chronic hemolytic anaemia like thalassemia.^{2,3} Endothelial cell damage and activation of oxidative stress due to hemolysis and iron overload might be contributory factors. There are only a few reported cases of MMS associated with Thalassemia, although other hemoglobinopathies like Sickle cell disease are a known risk factor for MMS.⁴⁻⁷

CASE

We report a rare case of beta thalassemia major associated with MMS presenting as acute ischemic stroke who was managed with encephaloduroarteriomyosynangiosis (EDAMS).

A 23-year-young male diagnosed as beta thalassemia major at 9 months of age, on intermittent blood transfusion till the age of 22 years followed by chemotherapy (thalidomide 50mg once daily). He showed good response on tablet thalidomide and was transfusion independent for the past 1 year as his hemoglobin level was maintained between 10.4 to 11.2 g/dl. He was not splenectomised and was on tablet deferasirox for iron chelation 800 mg once daily. Due to financial constraint of the patient, genetic mutation analysis could not be done and the diagnosis of Beta-thalassemia major was made on the basis of his HPLC findings and that of his parents.

He presented with acute confusional state (typing wrong number on his phone, inability to recognize relatives and

repeating same words) for 10-12 days. He also had dysarthria and one episode of urinary incontinence. On examination, he had mild pallor and hepatosplenomegaly.

MRI Brain showed multifocal small areas of restricted diffusion in left parietal cortex and subcortical white matter, left centrum semi ovale, corona radiata and in the periventricular white matter adjacent to the temporal horn of the left lateral ventricle suggestive of acute infarcts along with multifocal chronic infarcts (Figure 1A, B).

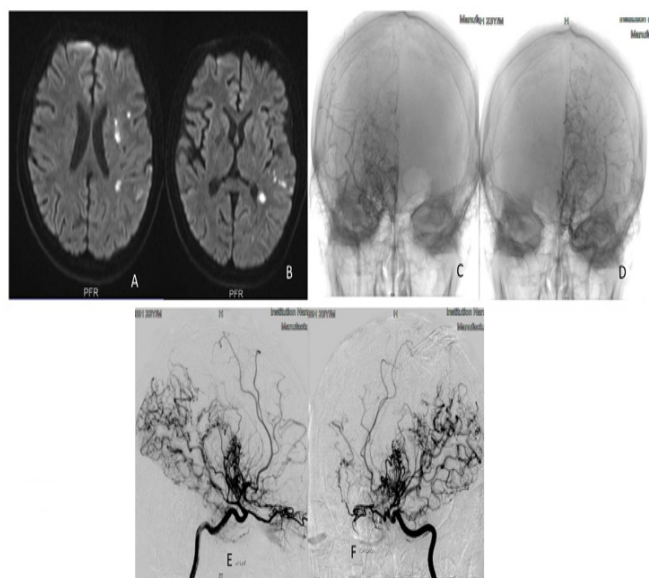


Figure 1. (A, B) MRI brain shows multifocal small areas of restricted diffusion in left parietal cortex and subcortical white matter, left centrum semi ovale, corona radiata and in the periventricular white matter adjacent to the temporal horn of the left lateral ventricle suggestive of acute infarcts along with multifocal chronic infarcts. (C-F) DSA shows bilateral supraclinoid ICA occlusion with rete/loco-regional collaterals supply reforming bilateral ACA, MCA territory with right PCA occlusion and loco-regional collaterals in posterior circulation reforming PCA territory suggestive of Moya Moya like phenomenon, Suzuki grade IV

DSA showed bilateral supraclinoid ICA occlusion with rete/loco-regional collaterals supply reforming bilateral ACA, MCA territory with right PCA occlusion and loco-regional collaterals in posterior circulation reforming PCA territory suggestive of Moya Moya like phenomenon, Suzuki grade IV (Figure 1C-F)

He was treated with single antiplatelet (acetyl salicylate 75 mg/day) and other supportive treatment. Additional work-up revealed a hemoglobin 9.6 g%, microcytic hypochromic anaemia and total bilirubin 3.4 mg/dl, with increased indirect fraction of 2.6 mg/dl and a direct fraction of 0.8 mg/dl. Homocysteine 4.7 umol/L, ESR 14 mm/hr, serum Ferritin 926 ng/ml. Subsequently, surgical intervention in the form of left sided (EDAMS) was done around 1 month after stroke, which he tolerated well. We plan to re-introduce thalidomide on follow-up.

DISCUSSION

The incidence of MMS along with β -thalassemia major is rare occurrence, with only a few cases documented in literature (Table). Most of the cases in literature are beta thalassemia major and only one case was alpha-thalassemia.⁸ The absence of β -globin subunits in thalassemia promotes the expression of pro-coagulant phospholipids like phosphatidylethanolamine, phosphatidylserine in red blood cells causing a hypercoagulable state mostly in patients not receiving blood transfusion. This leads to platelet aggregation, thromboembolism and atherosclerosis.^{17,18} Moreover, thalassemia may cause tissue hypoxia and hypertrophic vascular endothelium, leading to microvascular stenosis. There is evidence of increased angiogenesis-related factors, including endothelial colony-forming cells, several cytokines, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) in thalassemia.¹⁹ Increased

Table. Beta thalassemia with MMS

Serial no	Author/year	Age/sex	Neurological manifestation	MRI brain/MMS Suzuki grade (If available)	Follow up/remark
1	Inati A et al. ² / 2013	14 mon/F, Lebanese β -thalassemia major	At 3mon of age: Seizure At 14mon: episodes of left tonic posturing and mild hemiparesis	-Multiple acute infarcts: cortex of Lt frontal, parietal and occipital lobes, encephalomalacia in left superior parietal -MMS stage III	At 1 mon FU: asymptomatic with complete resolution of right hemiparesis
2	Marden et al. ³ / 2008	9 Y/ F hemoglobin Fairfax, beta thalassemia	Left hemiparesis	At 19mon: Right cerebral infarction, MRA: no characteristic findings of MMS MRI brain 7Y later: MMS	Chronic transfusion therapy and bone marrow transplantation, which were demonstrated to diminish risk of stroke in sickle-cell disease and -thalassemia may not halt progression of MMS as occurred in this case
3	Sunil et al. ⁴ / 2023	5Y/M Beta-thalassemia major	Left hemiparesis with loss of consciousness, History of multiple blood transfusions 4 months ago	MRI brain: subacute infarct of right parieto-temporal lobe.	Presented with a stroke due to MMS, and subsequent evaluation showed beta-thalassemia-showed importance of MRI brain and angiography
4	Das et at. ⁵ /2019	13Y/M/beta-thalassemia major 9Y/F/beta-thalassemia major 30Y/F/Hb E beta thalassemia 6Y/F/HbE trait	Hemiplegia/ Hemiparesis in 4 cases	3/4 cases: infarcts, 1 case with HbE- β -thalassemia: intracerebral hemorrhage.	Neither transfusion dependence nor the history of splenectomy was found to be associated with MMA development.

The table continues

Table 1. Beta thalassemia with MMS (The table continues)

5	Das et al. ⁶ / 2022	12 cases M: F=1:2 β-thalassemia major 4, β-thal- assemia carrier 4, HbE/β-thal- assemia in 2, HbE-trait in 1 and HbD/β-thalassemia in 1	Cerebral ischemic insult was predominant brain lesion and associated neurological manifestations were seen	MRI: Ischemic predominant: 91.7% cases -MMS	Mean follow-up of 28.3±13.9 months All medically managed 8.3%: New onset neuro-deficit and subsequent mortality, rest 91.7% no silent cerebral infarction
6	Doctor PN et al. ⁷ / 2018	25Y/F HbE-beta thalassemia	Choreoathetoid movements	-MRI Brain: No basal ganglia stroke -MMS	-PRBC transfusions, Aspirin -Secondary prophylaxis measures essential to prevent progression or recurrence
7	Zhu et al. ⁸ /2022	43Y/M alpha-thalassemia	Headache, dizziness and nausea.	MMS with aneurysm rupture and bleeding Haemorrhage from ventricular system and localized white matter hypodensity in left frontal lobe	Cerebral aneurysm embolization At 1 month post discharge, CT confirmed that each ventricle was unobstructed. Patients with MMS should undergo extracranial and intracranial revascularization as soon as possible.
8	El Beltage et al. ⁹ / 2014	16Y/F/ β-thalassemia intermedia	Headaches for 2Y, Recurrent focal seizures	Cranial MRI and MRA: Bilateral focal hyperintensities on FLAIR images with cortical, subcortical, sulcal, periventricular and anterior internal border zone. -Ivy sign -MMS	Development and degree of the ivy sign may be used as a predictor for developing symptomatic CNS ischemia
9	Parker et al. ¹⁰ / 2009	15Y/M, Cambodian, HbE/b-thalassemia	-No neurological manifestation -GH deficiency, MRI performed in view of GH deficiency	Left MMS	18mon later: no abnormal neurological findings
10	Mukherjee et al. ¹¹ / 1995	5-½ /F, b-thalassemia major	2-year history of alternating hemiplegia, Two years later, tonic clonic seizures on the left side, which progressed to intermittent left sided hemiplegia	MMS	-
11	Sanefuji et al. ¹² / 2006	14Y/F Japanese, beta-Thalassemia intermedia	One month after splenectomy, had episodes of transient right hemiparesis, headaches, and general malaise	MMS	Not clear whether MMS occurred before or after the splenectomy
12	Shaukat et al. ¹³ / 2025	6Y/F/ beta thalassemia major	Recurrent seizures for 3Y, dysarthria, difficulty walking 15 days prior, headaches and vertigo for 2 months	-Subacute ischemic infarct in the left occipital lobe. -Acute infarct with postischemic hyperperfusion and adjacent cortical laminar necrosis in left occipital lobe -Stage III MMD	6 months: No new neurological deficit Neurosurgery referral for consideration of surgical intervention
13	Vikhe VB et al. ¹⁴ / 2021	16Y/M/ Beta-thalassemia major	-Old history of ischemic stroke -Right hemiparesis, recurrent seizures	MRI: Right MCA, ACA territory acute non-haemorrhagic infarcts -MMS	Blood transfusions and antiplatelet therapy Transfusion dependency in beta thalassemia major might not be able to prevent progression of MMS
14	Kumar N et al. ¹⁵ / 2024	7Y/M/ Beta thalassemia major	Right upper limb monoparesis, focal seizures, right upper motor neuron type facial nerve palsy.	CECT head: Left ACA and MCA territory infarct	-Aspirin, valproate, blood transfusion -Monoparesis resolved over 1 week -No focal neurological deficits/ seizures till 6 months of follow-up
15	Sarkar et al. ¹⁶ / 2016	11Y/M HbE/beta thalassemia	Recurrent and progressive hemiplegia, Right hemiplegia for 1 year, left hemiplegia for 1 month	-MRI Brain: Encephalomalacia in bilateral cerebral hemisphere (left>right), Old infarct of left basal ganglia and periventricular white matter, -MMS	Children with thalassemia should be screened for future risk of MMS

Mon: Month, MRI: Magnetic resonance imaging, MMS: Moya Moya syndrome, CT: Computed tomography, FU: Follow up, Y: Years, PRBC : Packed red blood cell, ACA: Anterior cerebral artery, MCA: Middle cerebral artery, MRA: Magnetic resonance angiography, CECT: Contrast enhanced computed tomography, FLAIR: Fluid attenuated inversion recovery, GH: Growth hormone

bFGF levels may stimulate arterial growth and transforming growth factor beta-1 (TGFB1) mediates neovascularization, contributing to the pathogenesis of MMS.²⁰ High serum ferritin levels ≥1000 mg/L in itself is a risk factor.²¹

Thalidomide has immunomodulating and anti-angiogenic properties and induces gamma-globin gene expression to increase the proliferation of erythroid cells. It represses cytokine-induced nuclear factor κB, tumor necrosis factor-

alpha, vascular endothelial growth factor, and prostaglandin E2 synthesis, and increases the reactive oxygen species ROS p38 MAPK (mitogen-activated protein kinases) signalling pathway.²²

Thalidomide is found to cause deep vein thrombosis in 22.5% of adult patients with multiple myeloma and 2.3% in those with nononcologic indications. Thrombotic events in children are known to be uncommon.²³ Thromboembolic events occur with increased frequency in mostly in thalidomide combinations with other drugs, including steroids and particularly anthracycline-based chemotherapy. However, there is a low incidence of thrombosis with single-agent thalidomide treatment.²⁴ In case of any stroke symptom, immediate neuroimaging facilitates early diagnosis of MMS to prevent future strokes or transient ischemic attacks. There is no literature of genetics of MMS associated with thalassemia. Our case is unique as apart from MMS being rare in thalassemia, very few such cases undergo surgical revascularization management.

CONCLUSION

MMS may develop insidiously in patients of thalassemia and result in debilitating neurological manifestations like stroke or transient ischemic attack. Any neurological symptom indicating possible stroke warrants prompt investigation in the form of MRI Brain and angiography of head and neck vessels in order to exclude MMS or other occlusive arteriopathy. Apart from medical management with antiplatelet, surgical revascularization may be beneficial for cerebral perfusion to prevent further ischemic events.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

Concept: GRM, VG Design: GRM, VG Data Collection and/or Processing: GRM Analysis and/or Interpretation: SN, CG Literature Review: GRM Writing the Article: GRM Critical Review: CS, VG.

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