J Korean Med Sci. 2024 Jan 15;39(2):e5
https://doi.org/10.3346/jkms.2024.39.e5
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Oncology & Hematology

A Multicenter Analysis of Clinical Features and Long-Term Outcomes of POEMS Syndrome in Korea

Hye Won Kook [1], **Ji Eun Jang** [1], **Chang-Ki Min** [2], **Dok Hyun Yoon** [3], **Kihyun Kim** [4], **Soo-Mee Bang** [5], **Yong Park** [6], **Jae Hoon Lee** [7], **Sung-Soo Yoon** [8] and **Jin Seok Kim** [1]

[1]Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[3]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[4]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[5]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[6]Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea
[7]Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Korea
[8]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Received: Jun 25, 2023
Accepted: Oct 24, 2023
Published online: Nov 30, 2023

Address for Correspondence:
Jin Seok Kim, MD, PhD
Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: hemakim@yuhs.ac

Sung-Soo Yoon, MD, PhD
Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: ssysmc@snu.ac.kr

ORCID iDs
Hye Won Kook
https://orcid.org/0000-0002-3544-0060
Ji Eun Jang
https://orcid.org/0000-0001-8832-1412
Chang-Ki Min
https://orcid.org/0000-0002-1940-0392
Dok Hyun Yoon
https://orcid.org/0000-0002-8289-3548
Kihyun Kim
https://orcid.org/0000-0002-5878-8895

ABSTRACT

Background: POEMS syndrome is a rare form of plasma cell dyscrasia characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes. Owing to its low incidence, there are few reports regarding this syndrome. This multicenter study included 84 patients diagnosed with POEMS syndrome in South Korea.
Methods: We retrospectively evaluated 84 patients diagnosed with POEMS syndrome at 8 hospitals in South Korea between January 2000 and October 2022. The clinical characteristics and treatment outcomes were analyzed.
Results: The median patient age was 53 years (range, 26–77 years), and 63.1% of the patients were male. All patients had peripheral neuropathy, and 81 (96.4%) had monoclonal plasma cell proliferation. Plasma vascular endothelial growth factor levels were available for 32 patients with a median of 821 pg/mL (range, 26–12,900 pg/mL). Other common features included skin changes (54.2%), volume overload (71.4%), and organomegaly (72.6%). Of the 84 patients, 75 received initial treatment (local radiotherapy, 6 [8.0%]; chemotherapy, 17 [22.7%]; both chemotherapy and local radiotherapy, 9 [12.0%]), upfront autologous stem cell transplantation (ASCT), 43 (57.3%; with induction chemotherapy, n = 12, 16.0%; without induction chemotherapy, n = 31, 41.3%). The median follow-up duration was 40.7 months. The 5-year overall survival (OS) was 78%, and the 5-year progression-free survival (PFS) was 55%. Patients who underwent upfront ASCT and were diagnosed after 2014 had a longer OS and PFS.
Conclusion: The demographics of Korean patients with POEMS syndrome were similar to those reported previously. Because of the introduction of new treatment agents and the reduced rate of transplant-related mortality related to ASCT, the treatment outcomes of Korean patients with POEMS syndrome have improved in recent years.

Keywords: POEMS Syndrome; Long-Term Outcome; Autologous Stem Cell Transplantation

Soo-Mee Bang
https://orcid.org/0000-0002-0938-3007
Yong Park
https://orcid.org/0000-0001-7909-6639
Jae Hoon Lee
https://orcid.org/0000-0002-1342-3104
Sung-Soo Yoon
https://orcid.org/0000-0003-2591-7459
Jin Seok Kim
https://orcid.org/0000-0001-8986-8436

Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Kook HW, Kim JS. Data curation: Kook HW, Jang JE. Investigation: Kook HW, Jang JE, Min CK, Yoon DH, Kim K, Bang SM, Park Y, Lee JH, Yoon SS, Kim JS. Methodology: Kook HW, Jang JE, Min CK, Yoon DH, Kim K, Bang SM, Park Y, Lee JH, Yoon SS, Kim JS. Writing - original draft: Kook HW. Writing - review & editing: Kook HW, Jang JE, Min CK, Yoon DH, Kim K, Bang SM, Park Y, Lee JH, Yoon SS, Kim JS.

INTRODUCTION

POEMS syndrome is a rare paraneoplastic syndrome characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin lesions; however, its pathogenesis remains poorly understood. It was presumed that vascular endothelial growth factor (VEGF), a cytokine produced by plasma cells, plays an important role in the development of the disease.[1] Physiological effects of VEGF include neovascularization and increasing vascular permeability, which could result in organomegaly and volume overload, including ascites, pleural effusion, pericardial effusion, peripheral edema, and papilledema. However, based on the unsuccessful results of anti-VEGF therapy in POEMS syndrome, VEGF may not be the primary driver of the disease.[2,3] Nevertheless, VEGF is still considered the cytokine that reflects the activity of the disease.[4]

Reports regarding POEMS syndrome are limited because of its low incidence and the difficulty in diagnosis. Systemic features of the syndrome, including endocrinopathies and signs of volume overload, may be overlooked owing to other comorbidities. The neurologic symptoms, in the absence of careful examination of associated features, might lead to the diagnosis of chronic inflammatory demyelinating polyneuropathy. In other cases, based on the abnormal results of serum or urine protein electrophoresis and immunofixation, a diagnosis of monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or multiple myeloma could be made. Therefore, a multidisciplinary approach by hematologists, neurologists, and endocrinologists is essential for accurate and early diagnosis of POEMS syndrome.

There is no consensus regarding the treatment of this syndrome. In the 1980s, patients were primarily treated with corticosteroids.[5] Since the 1990s, treatment strategies based on targeting the underlying clonal plasma cells have benefited patients with POEMS syndrome. These therapeutic agents include alkylators, immunomodulatory drugs, and proteasome inhibitors, and they have shown promising results.[6] Autologous stem cell transplantation (ASCT) also has been performed with encouraging outcomes.[7] Recently, different approaches, based on the risk at diagnosis or the presence of disseminated bone marrow involvement, have been suggested.[8-11]

To better understand and identify the disease characteristics, long-term outcomes, and appropriate risk factors, we conducted a multicenter retrospective study of patients with POEMS syndrome in South Korea.

METHODS

Patients

We retrospectively reviewed patients diagnosed with POEMS syndrome at 8 hospitals in South Korea between January 2000 and October 2022. The diagnosis of POEMS syndrome was made according to internationally recognized criteria.[9] Clinical feature data; laboratory, radiological, neurological, and pathological data; and treatment outcome data were collected.

Responses to treatment based on previously reported measures,[12,13] comprised mainly 3 domains. Clinical response comprised the following 2 categories: clinical improvement, and no clinical improvement/progression. Clinical progression was defined as any worsening of

POEMS syndrome features. Hematologic response comprised the following categories based on the modified International Myeloma Working Group criteria[14]: 1) complete response (CR_H) was defined as negative results for bone marrow and negative immunofixation analysis of serum and urine. 2) A very good partial response was defined as a 90% reduction in monoclonal protein or immunofixation positivity, as long as monoclonal protein was at least 0.5 g/dL at baseline. 3) Partial response was defined as a 50% reduction in monoclonal protein or immunofixation-positivity, as long as the baseline monoclonal protein level was at least 1.0 g/dL. 4) No response referred to conditions that did not fulfill the above criteria. 5) Progression was defined as the re-emergence of serum/urine monoclonal protein if it was undetectable or increased by 25% from the lowest post-treatment value. Plasma VEGF levels were used to assess biochemical responses. The responses were defined as follows: complete remission (CR_V), normalization of levels; partial response, > 50% reduction in serum VEGF levels; no response, does not fulfill the above criteria; not evaluable, initial serum VEGF level not raised/not evaluated; and progression, persistent serum VEGF level elevation by more than that of 2 recordings from a previously normal result or persistent serum VEGF level rise by > 50% from the lowest post-treatment value of more than 2 recordings.

Statistical analyses

All non-normally distributed parameters are presented as medians with first and third quartiles. An independent two-sample *t*-test or Mann-Whitney *U* test was employed in accordance with the distribution of continuous variables. The χ^2 test or Fischer's exact test was used to compare categorical variables. Progression-free survival (PFS) was defined as the time from the POEMS syndrome diagnosis to the first relapse/progression or death. Overall survival (OS) was measured from the date of confirmed diagnosis to the date of death for any reason or to the last follow-up. OS and PFS were estimated using the Kaplan-Meier method, and a log-rank test was performed to compare the outcomes between the groups. A Cox proportional hazards regression model was used to determine factors that had significant effects on survival and disease progression. Statistical significance was set at *P* value < 0.05. All statistical analyses were performed using the SPSS software (version 26.0; IBM SPSS Statistics, Armonk, NY, USA).

Ethics statement

This study was approved by the Institutional Review Boards (IRBs) of the respective institutions, including the Yonsei University College of Medicine (IRB No. 4-2023-0512), and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study.

RESULTS

Patient characteristics

Overall, 84 patients (median age: 53 years [range, 26–77 years]; male: 63.1% [n = 53]) were included in the study. The main clinical characteristics of the eligible patients are summarized in **Table 1**.[15-17] The median time from neurological symptom presentation to the diagnosis of POEMS syndrome was 173 days (range, 0–3,969 days). All 84 patients (100%) had peripheral neuropathy. Sixty-one patients (72.6%) had organomegaly, 56 (69.1%) had endocrinopathy, 81 (96.4%) presented with monoclonal gammopathy, and 45 (54.2%) showed skin changes. Sixty patients (71.4%) had volume overload, and 15 (18.3%) had Castleman disease. Plasma VEGF levels were measured in 32 patients, with a median

https://doi.org/10.3346/jkms.2024.39.e5

of 821 pg/mL (range, 26–12,900 pg/mL). Among them, 21 patients had high plasma VEGF levels (>200 pg/mL). Twenty-four patients (41.4% of patients assessed using transthoracic echocardiography) presented with pulmonary hypertension. Twenty-three patients (62.2% of patients with available pulmonary function test results) had decreased carbon monoxide diffusing capacity of the lungs (DLCO). The median initial serum monoclonal protein concentration of all patients was 0.10 g/dL (range, 0.00–1.66 g/dL). Eighty-one patients (96.4%) showed positive serum immunofixation results; among them, 31 (38.2%) had immunoglobulin G, 39 (48.1%) had immunoglobulin A, and 1 (1.2%) had a biclonal type. Seventy-five patients (92.5%) had lambda light chain restriction, 2 patients (2.6%) had kappa paraprotein, and 4 patients (5.2%) had a biclonal pattern. Three patients (3.6%) presented with negative results on serum protein electrophoresis and immunofixation. Serum-free light chains were measured in 61 (72.6%) patients, and an abnormal kappa:lambda ratio was detected in 11 (18.0%) patients. Of the 76 patients with available bone marrow study results at diagnosis, 9 (11.8%) showed > 10% plasma cells in the bone marrow. The demographics and clinical characteristics of the patients were compared with those previously reported from Japan, the United Kingdom (UK), and the United States (US) in **Table 1**.[15-17]

The median white blood cell count at diagnosis was 6.92×10^9/L (range, 1.37–26.9×10^9/L). The median platelet count at diagnosis was 361×10^9/L (range, 45–643×10^9/L), and the median hemoglobin concentration was 13.2 g/dL (range, 5.0–18.0 g/dL). The median estimated glomerular filtration rate (eGFR) was 86 mL/min/1.73 m^2 (range, 24–175 mL/min/1.73 m^2), and the median albumin level was 3.6 g/dL (range, 1.6–4.8 g/dL). Five patients (7.0%) had lactate dehydrogenase (LDH) levels higher than the upper limit of each institution. The median LDH level was 169 U/L (range, 78–475 U/L).

Elevated plasma VEGF levels were significantly associated with the presence of ascites (P = 0.02) and overall volume overload (P = 0.006) but not with peripheral edema (P = 0.640), pleural effusion (P = 0.174), pericardial effusion (P = 0.135), or pulmonary hypertension (P = 0.248). (**Supplementary Table 1**)

Treatment and outcome

Of the 84 patients, 75 were treated at the institution where they were diagnosed and were included in the outcome analysis. The first-line treatments for these patients are presented in **Table 2**. Six patients (8.0%) received local radiotherapy alone, 17 (22.7%) received chemotherapy alone, and 9 (12.0%) underwent both chemotherapy and local radiotherapy. The remaining 43 (57.3%) patients underwent upfront ASCT.

Among the patients who received frontline chemotherapy (n = 38), detailed information about the chemotherapy regimen was available for 37 patients. Sixteen patients (43.2%) were treated with melphalan-based regimens, 5 (13.5%) with thalidomide-based regimens, 2 (5.4%) with bortezomib-based regimens, and 14 (37.8%) with other drugs, including cyclophosphamide plus dexamethasone (n = 11, 29.7%) and vincristine/doxorubicin/dexamethasone combination chemotherapy (n = 3, 8.1%). None of the patients were treated with lenalidomide-based regimens as first-line therapy because of the Korean drug approval and reimbursement guidelines.

The median follow-up period for all patients was 40.7 months (range, 1–207 months). The CR_H rate, CR_V rate, and clinical improvement rate were 67.2%, 70.0%, and 82.0%, respectively (**Table 3**). The best overall response rate was 98.4% for hematologic response

https://doi.org/10.3346/jkms.2024.39.e5

Table 1. The main clinical characteristics of all patients

Characteristics	Present study, South Korea, % (n = 84)	Lunn et al.[16], United Kingdom, % (n = 100)	Kuwabara et al.[15], Japan, % (n = 167)	Dispenzieri et al.[17], United States, % (n = 99)
Age, yr, median (range)	53 (26–77)	56 (31–84)	54 (21–84)	51 (30–83)
Male sex	63	68	59	63
From symptom to diagnosis, day, median (range)	173 (0–3,969)	450 (30–2,310)	NA	NA
Polyneuropathy				
Peripheral neuropathy	100	96	100	100
Raised CSF protein	94 (n = 36)	100 (n = 65)	NA	100
Monoclonal plasma cell disorder	96.4			
Serum M protein, g/dL, median (range)	0.10 (0.00 – 1.66)	55	86	54
Serum immunofixation		78		
IgG-lambda	37 (n = 81)	44	IgG/IgA/IgM, 52/47/1	IgG/IgA/IgM, 47/52/1
IgA-lambda	48 (n = 81)	53	Kappa:lambda, 8/92	Kappa:lambda, 0/100
Biclonal	7 (n = 81)	3		
IgG-kappa	1 (n = 81)	2		
IgA-kappa	0 (n = 81)	0		
Kappa:lambda ratio				
Normal kappa:lambda	82 (n = 61)	78 (n = 83)	NA	NA
> Kappa:lambda	18 (n = 61)	17 (n = 83)		
< Kappa:lambda	0 (n = 61)	5 (n = 83)		
BM abnormality				
0–4% PC	53 (n = 76)	29 (n = 86)	NA	NA
5–9% PC	36 (n = 76)	17 (n = 86)		
> 10% PC	12 (n = 76)	18 (n = 86)		
BM plasma cells, %, median (range)	4.2 (0–25.3)	NA	2.4 (0–30)	NA
Castleman disease	18 (n = 82)	14	11	73 (n = 15)
Bone lesions	83	81	58	97
Sclerotic	81	55	81	47
Lytic	26	15	11	51
Mixed sclerotic and lytic	5	30	7	2
VEGF, pg/mL, median (range)	821 (26–12,900) Plasma	3,594 (200–30,101) Serum	418 (16–6,340) Plasma 3,230 (72–31,300) Serum	NA
Endocrine abnormality	69 (n = 81)	68	65	67
Gonadal axis abnormality	15 (n = 24)	NA	21	55
Hypothyroidism	52 (n = 60)	NA	35	14
DM	44 (n = 80)	NA	13	3
Prolactinoma	8 (n = 26)	NA	8	5
Adrenal axis abnormality	12 (n = 22)	NA	17	16
Panhypopituitarism	2 (n = 18)	NA	NA	NA
Organomegaly	73	63	76	50
Splenomegaly	63	31	59	22
Hepatomegaly	32	23	45	24
Lymphadenopathy	32	42	35	26
Skin abnormalities	54 (n = 83)	69	84	68
Hyperpigmentation	44 (n = 83)	25	68	46
Hypertrichosis	7 (n = 83)	20	19	26
Hirsutism	12 (n = 83)	NA	NA	NA
Volume overload	71	70	81	29
Peripheral edema	35	66	65	24
Pericardial effusion	27	NA	22	NA
Pleural effusion	39	16	49	3
Ascites	30	6	43	7
Papilledema	47 (n = 51)	30	24	29
Plasmacytoma	25	90 (n = 42)	NA	NA
Other				
Pulmonary hypertension	41 (n = 58)	28 (n = 53)	13	5
Decreased DLCO	62 (n = 57)	NA	NA	NA

CSF = cerebrospinal fluid, BM = bone marrow, PC = plasma cell, VEGF = vascular endothelial growth factor, DM = diabetes mellitus, DLCO = diffuse lung capacity for carbon monoxide, NA = not available.

https://doi.org/10.3346/jkms.2024.39.e5

Table 2. First line treatments for all treated patients

1st line treatment	Treated, total (N = 75)
Treatment types	
Radiation only	6/75 (8.0)
Chemotherapy only	17/75 (22.7)
Radiation + Chemotherapy	9/75 (12.0)
Chemotherapy + ASCT	12/75 (16.0)
Upfront ASCT	31/75 (41.3)
Chemotherapy regimen	
Melphalan	16/37 (43.2)
Thalidomide	5/37 (13.5)
Lenalidomide	0/37 (0.0)
Bortezomib	2/37 (5.4)
Others	14/37 (37.8)

ASCT = autologous stem cell transplantation.

Table 3. Response to treatment in the three domains of response evaluation.

Response	All treated (n = 75)	ASCT (n = 43)
Hematologic response		
CR	43/64 (67.2)	25/38 (65.8)
VGPR	14/64 (21.9)	9/38 (23.7)
PR	6/64 (9.4)	4/38 (10.5)
SD	1/64 (1.6)	0/38 (0.0)
NR	0/64 (0.0)	0/38 (0.0)
VEGF response		
CR	14/20 (70.0)	14/19 (73.7)
PR	4/20 (20.0)	3/19 (15.8)
SD	1/20 (5.0)	1/19 (5.3)
NR	1/20 (5.0)	1/19 (5.3)
Clinical response		
Clinical improvement	41/50 (82.0)	34/39 (87.2)
No clinical improvement/progression	9/50 (18.0)	5/39 (12.8)

ASCT = autologous stem cell transplantation, CR = complete response, VGPR = very good partial response, PR = partial response, SD = stable disease, NR = no response, VEGF = vascular endothelial growth factor.

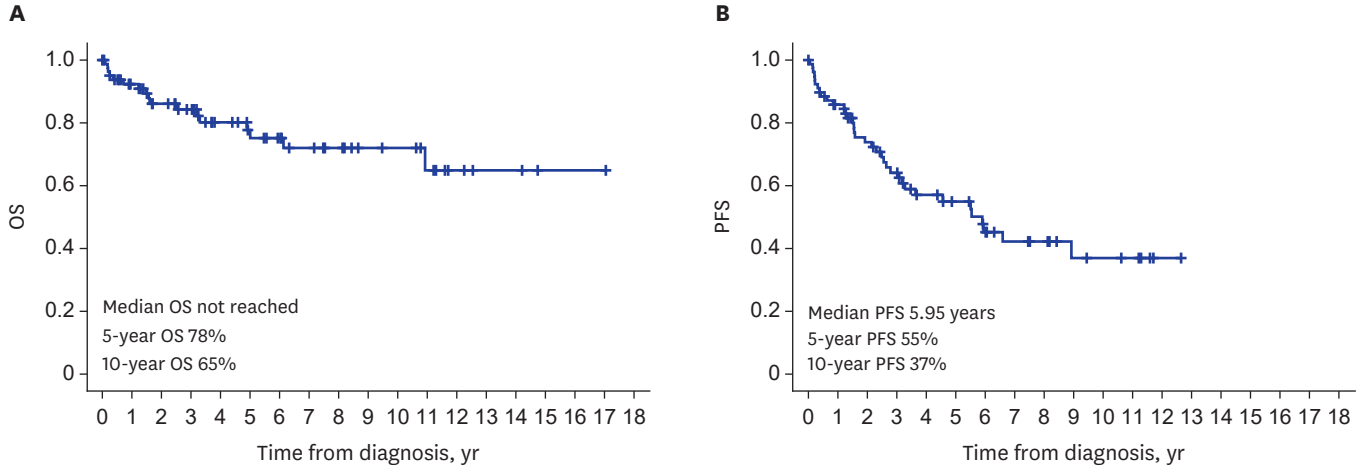

Fig. 1. OS (**A**) and PFS (**B**) of all treated patients (n = 75).
OS = overall survival, PFS = progression-free survival.

and 90.0% for VEGF response. The median OS was not reached (5-year OS: 78%; 10-year OS: 65%), and the median PFS was 71.4 months (5-year PFS: 55%; 10-year PFS: 37%) (**Fig. 1**). High LDH at diagnosis was associated with a trend towards for longer OS (**Supplementary Table 2**). According to the diagnosis period, patients diagnosed after 2014 showed a trend of longer PFS than did the patients diagnosed before December 2013 (**Supplementary**

https://doi.org/10.3346/jkms.2024.39.e5

Fig. 1). The treatment and chemotherapy regimen used based on the diagnosis period is demonstrated in **Supplementary Table 3**.

Upfront ASCT

Of the 43 patients who underwent upfront ASCT, 31 (41.3%) received ASCT without previous induction chemotherapy, and 12 (16.0%) were treated with induction chemotherapy before ASCT. The median follow-up period for patients who underwent upfront ASCT was 37.5 months (range, 1–152 months). The stem cell mobilization method was available in 42 patients. Twenty-five patients were treated with the granulocyte colony-stimulating factor for stem cell mobilization, while 17 patients were treated with cyclophosphamide + granulocyte colony-stimulating factor. The median infused CD34 cell count was 5.09×10^6 cells/kg (range, 2.12–48.30 × 10^6 cells/kg), and the conditioning regimen was high-dose melphalan at 140–200 mg/m^2 according to kidney function. VEGF responses were detected in 19 patients. Fourteen patients (73.7%) achieved complete response, and 3 patients (15.8%) achieved partial response, adding up to a response rate of 89.5%. One patient (5.3%) remained stable disease, and 1 (5.3%) patient showed no response. A hematological response was observed in 38 patients; of these, 25 (65.8%) achieved a complete response, 9 (23.7%) achieved a very good partial response, and 4 (10.5%) achieved a partial response. The clinical improvement rate was 87.2% (**Table 3**). A brief comparison of the outcomes of patients who received upfront ASCT with those of previous reports is summarized in **Table 4**.[12,18-22] Of the 43 patients, 8 (18.6%) died; of these, 5 (11.6%) died of transplant-related mortality (TRM), including infections such as pneumonia. Age > 50 years was the only factor that showed a tendency toward increasing TRM ($P = 0.071$), while ascites ($P = 0.792$), peripheral edema ($P = 0.161$), pleural effusion ($P = 0.232$), pericardial effusion ($P = 0.278$), pulmonary hypertension ($P = 0.581$), eGFR < 30 mL/min/1.73 m^2 ($P = 0.245$), high LDH levels ($P = 0.247$), and albumin < 3.2 g/dL ($P = 0.416$) were not significantly associated with an increased risk of TRM (**Supplementary Table 4**).

Subgroup analysis of the 43 patients who received upfront ASCT showed that there was a tendency of poor OS in patients with eGFR < 30 mL/min/1.73 m^2 than in patients with eGFR > 30 mL/min/1.73 m^2 ($P = 0.078$) (**Fig. 2**). Also, recent diagnosis year > 2014 was associated with a trend for longer PFS ($P = 0.056$). In our study, there were no significant differences in OS and PFS according to plasma VEGF > 200 pg/mL ($P = 0.531$ and $P = 0.570$), age > 50 years at diagnosis ($P = 0.933$ and $P = 0.488$), albumin < 3.2 g/dL ($P = 0.586$ and $P = 0.172$), and volume overload ($P = 0.860$ and $P = 0.137$) (**Supplementary Table 5**). The TRM rates were 16.1% (5/31) and 0.0% (0/12) for patients diagnosed before December 2013 and after January 2014, respectively ($P = 0.177$).

Table 4. Frontline autologous stem cell transplantation in POEMS syndrome

Characteristics	Number	TRM	ES	5-year PFS	5-year OS	CR_H	CR_V	CR_{PET}	Clinical/ Neurological improvement	Induction chemotherapy pre-ASCT
CIBMTR	331	0.90%	15%	72%	91%	-	-	-	-	45%
PUMCH	138	2%	15%	76%	94%	50%	72%	-	90%	23%
EBMT	127	2%	23%	74%	89%	49%	-	-	-	87%
Japanese TRUMP	95	0%	16%	65%	89%	39%	86%	-	-	86%
Mayo	59	2%	37%	75%	94%	57%	48%	17%	92%	47%
UCLH	42	2%	7%	77%	90%	33%	64%	90%	95%	38%
Present study	43	9%	7%	59%	85%	66%	74%	-	87%	28%

CIBMTR = Center for International Blood and Marrow Transplant Research, CR_H = complete hematological response, CR_V = complete vascular endothelial growth factor (VEGF) response, CR_{PET} = complete response on PET scan, EBMT = European Society for Blood and Marrow Transplantation, ES = engraftment syndrome, OS = overall survival, PFS = progression-free survival, PUMCH = Peking Union Medical College Hospital (China), TRM = transplant-related mortality, TRUMP = transplant registry unified management program, UCLH = University College London Hospital.

https://doi.org/10.3346/jkms.2024.39.e5

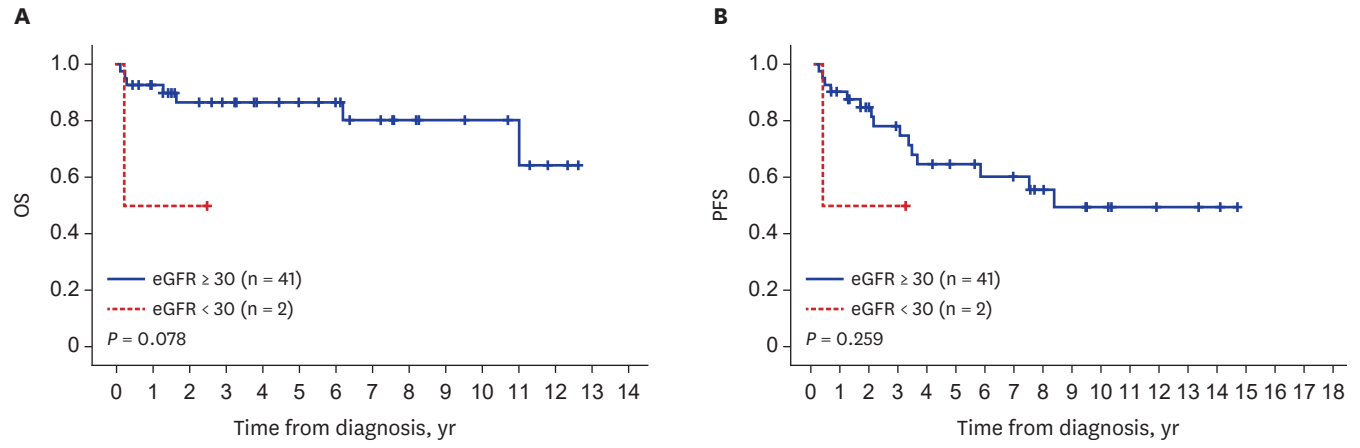

Fig. 2. Overall survival (**A**) and progression-free survival (**B**) of patients who underwent autologous stem cell transplantation, stratified by eGFR (cutoff: 30 mL/min/1.73 m^2; n = 43).
eGFR = estimated glomerular filtration rate.

Risk stratification

Patients were stratified into low-, intermediate-, and high-risk groups according to age, presence of volume overload, and kidney function, as suggested by the Peking University group.[10] In our cohort, the patient prognosis could not be demonstrated by this risk stratification (**Supplementary Fig. 2**). In the high-risk group, there was a tendency toward longer OS and PFS in the ASCT group than in the non-ASCT group (**Fig. 3**).

The role of positron emission tomography-computed tomography (PET-CT) in diagnosis

Overall, 35 patients underwent PET-CT at diagnosis. Among them, 25 (71.4%) revealed bone lesions, 7 (20.0%) revealed Castleman disease, 7 (20.0%) revealed organomegaly, and 10 (28.5%) showed volume overload. Among the 25 patients who had revealed bone lesions on PET-CT, 3 did not reveal abnormal bone lesions on bone scintigraphy.

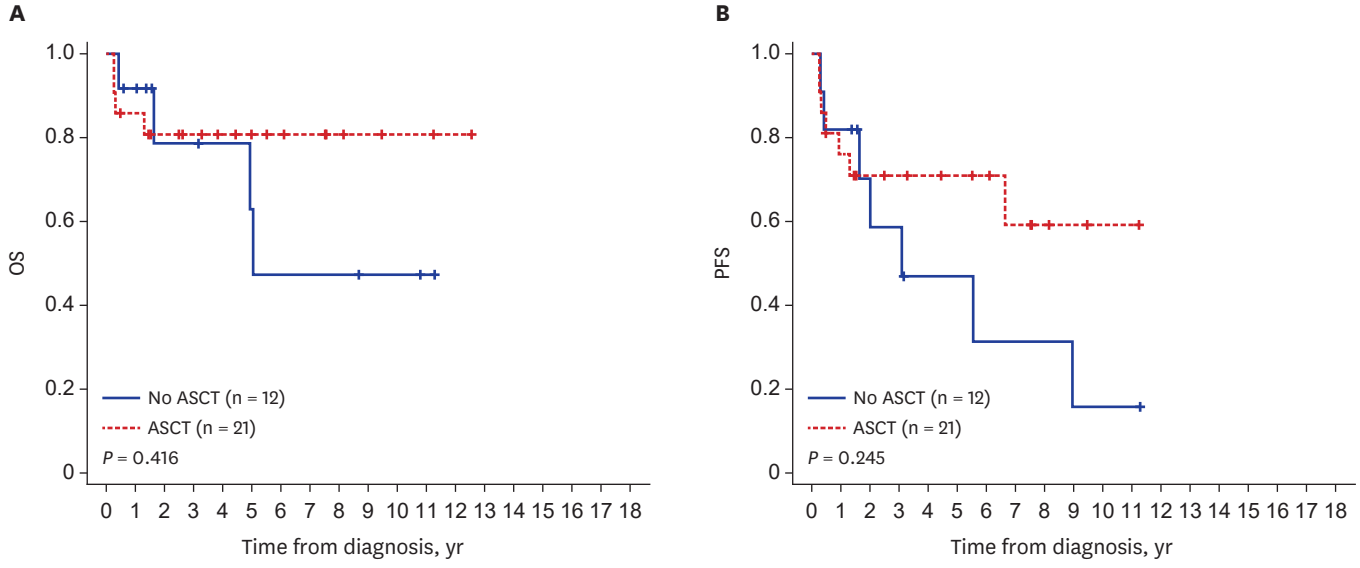

Fig. 3. Overall survival (**A**) and progression-free survival (**B**) of high-risk group patients by ASCT (n = 31).
ASCT = autologous stem cell transplantation.

https://doi.org/10.3346/jkms.2024.39.e5

Biopsies were performed in 19 of the 25 patients with bone lesions detected using PET-CT. Of these, 16 patients were pathologically confirmed to have plasmacytoma, and 3 had failed biopsy results. In 12 (75.0%) patients, plasmacytomas were detected using PET-CT, and in 9 (56.2%), plasmacytomas were detected using bone scintigraphy.

DISCUSSION

This multicenter study demonstrated the current status of POEMS syndrome in South Korea. With a median follow-up period of 40.7 months and participation from multiple institutions, this is the first study to report demographics and treatment outcomes of POEMS syndrome in South Korea. The demographics and clinical characteristics of the patients with POEMS syndrome were similar to those previously reported by Japanese, UK, and US groups.[15-17] The incidence of pleural effusion and ascites was higher in our report than in the UK and US reports.[16,17] Presumably, the previous studies conducted in other countries may not have thoroughly assessed these characteristics. However, the recent increased awareness of this disease and rigorous radiological investigations of volume overload might have led to the easy detection of volume overload in Korean patients. The relatively low percentage of patients with hypertrichosis in the present study may be due to the absence of detailed medical records on the amount of hair.

The diagnosis of POEMS syndrome required keen observation of patients with related symptoms, with a median duration of 173 days from neurological symptoms to diagnosis, which was shorter than that reported previously by the UK group (450 days).[16] This might also be related to the recent increased awareness of this disease.

In our cohort, only half the patients had the results of plasma VEGF levels available at diagnosis. Because this study included patients over 20 years old, patients diagnosed earlier had no VEGF analysis results. Pre-treatment VEGF data were available for 89.0% of the Japanese group and 58.1% of the UK group.[15,16] Elevated VEGF levels are one of the three other major criteria for diagnosing POEMS syndrome and are a useful tool for evaluating disease status and treatment response.[4,14] Elevated VEGF levels were significantly related to ascites development and volume overload in this study. This finding may be well understood with regard to the physiological effects of VEGF, which induces neovascularization and increases vascular permeability. Although a clinical trial with anti-VEGF therapy in POEMS syndrome did not show promising results,[2,3] VEGF is still regarded as a cytokine that represents the activity of the disease.[4] Therefore, the detection of VEGF levels should be emphasized for patients suspected of having POEMS syndrome. In addition, blood specimens for VEGF detection should be carefully identified because the reference ranges of VEGF in plasma and serum are different, with serum VEGF levels usually 10–50 times higher than plasma VEGF levels.[23]

As the pathophysiology of POEMS syndrome is poorly understood and there are no known molecular or genetic risk factors that predict OS, most risk stratifications for POEMS syndrome are based on clinical presentation. The Peking University group proposed a risk stratification method based on age, eGFR, and the existence of pleural effusion.[10] There was an attempt to validate this prognostic system in a Mayo Clinic cohort, in which the prognostic value between the intermediate- and low-risk groups was not clearly demonstrated.[24] However, this risk stratification method could not be validated in our cohort. In our study,

age at diagnosis > 50 years was the only factor that showed a trend toward high TRM in patients undergoing ASCT. In addition, eGFR < 30 mL/min/1.73 m^2 was the only factor that showed a trend toward poor OS in patients undergoing ASCT. Notably, volume overload, including pleural effusion, pericardial effusion, and pulmonary hypertension, was not significantly associated with a high TRM or poor OS and PFS. In patients who were able to perform ASCT because they did not present with severe volume overload or severe pulmonary hypertension, the existence of volume overload or pulmonary hypertension was not considered a poor prognostic factor in this study. These results suggest that ASCT may improve treatment outcomes without increasing TRM in POEMS syndrome patients without severe volume overload or severe pulmonary hypertension. In other words, when concluding that volume overload and pulmonary hypertension are factors for poor prognosis, they should be limited to very severe cases that would make the patient intolerable to intensive treatment, such as ASCT. Appropriate prognostic factors predicting the outcomes of POEMS syndrome should be re-evaluated in a large population of patients who have received a similar intensity of treatment. Further analysis of our data for patients who received upfront ASCT revealed that several well-known factors related to worse outcomes, including albumin < 3.2 g/dL, pericardial effusion, pleural effusion, age > 50 years, pulmonary hypertension, and plasma VEGF > 200 pg/mL were not significant prognostic factors for worse OS and PFS. In other words, the aforementioned factors associated with worse outcomes may be overcome with upfront ASCT.

Changes in treatment strategies from steroid-based therapies to plasma cell-targeting treatments and the introduction of ASCT have enhanced the overall prognosis of POEMS syndrome.[25] In our study, recent diagnosis year > 2014 was associated with a trend for longer PFS in all treated patient groups and also in the ASCT group. Before December 2013, 11 patients (42.3%) were treated with conventional chemotherapies and 2 (7.7%) were treated with thalidomide. After January 2014, 3 patients (25.0%) were treated with conventional chemotherapies and 3 (25.0%) were treated with thalidomide. The total percentages of ASCT performance were similar in both patient groups diagnosed before December 2013 and after January 2014, which were 58.5% (31/53) and 54.5% (12/22), respectively. However, the TRM rates in both groups were 16.1% (5/31) and 0.0% (0/12), respectively. Therefore, we concluded that regimen changes from conventional cytotoxic drugs to immunomodulatory drugs and reduction of TRM incidence may have resulted in better treatment outcomes in POEMS syndrome.

Compared to that of previous reports, the 5-year PFS rate of 55% in our study was relatively inferior. This may be due to the limitations in selecting initial treatment agents for POEMS syndrome. Among the several new agents with anti–myeloma activity, lenalidomide is recommended for the initial treatment of POEMS syndrome by many guidelines because of its lack of neurotoxicity.[26] However, no patient received lenalidomide as a first-line therapy in our cohort. Therefore, lenalidomide and new targeted agents for multiple myeloma should be incorporated during the early phase of POEMS syndrome treatment in Korea to improve treatment outcomes.

Although local radiotherapy is effective for POEMS syndrome patients with localized plasmacytomas, immunomodulatory drugs such as lenalidomide and upfront ASCT for transplant-eligible patients are recommended for most patients with POEMS syndrome with advanced systemic involvement.[26] Compared to other reports on frontline ASCT in POEMS syndrome, our patients showed similar CR_H, CR_V, and clinical or neurological improvement.[12,18-22] However, the 5-year PFS and 5-year OS rates were relatively lower.

https://doi.org/10.3346/jkms.2024.39.e5

These results may be related to the low percentage of patients who received induction chemotherapy before ASCT and the relatively high rate of TRM (11.6%). Careful selection of candidates for ASCT and intensive supportive care during transplantation should be emphasized to improve ASCT outcomes in Korea.

PET-CT scanning should be routinely performed at diagnosis to detect plasmacytoma or Castleman disease in patients with POEMS syndrome because it is not easy to detect these lesions using bone scintigraphy or plain simple radiography. In this study, bone scintigraphy and PET-CT were complementary for the detection of plasmacytoma and osteosclerotic bone lesions. In addition, PET-CT is very helpful in deciding the site for biopsy because it can easily detect abnormal high-intensity sites that usually show no abnormal findings on bone scintigraphy. Organomegaly and volume overload can also be assessed using PET-CT at the time of diagnosis. As PET-CT is a good method for evaluating treatment responses, recent recommendations on POEMS syndrome have included PET-CT responses in the response criteria.[26]

The limitations of this study are primarily due to its retrospective nature. In retrospective analysis, there are various biases that may influence data acquisition and interpretation. The availability of pulmonary function test, transthoracic echocardiography, and PET-CT data at diagnosis differed by patients which led to a lack of results of DLCO, pericardial effusion, pulmonary hypertension, organomegaly and other diagnostic features. This might have biased the results when defining adequate prognostic factors. Also, the judgment on clinical improvement largely depended on the medical records of the physician, which could have resulted in biases on data collection. In addition, to analyze the treatment outcomes, all patients should be treated with homogeneous strategies. However, the applied treatments in this study were diverse because the treatment decision was made according to each institution's guidelines. Furthermore, some internationally recommended treatment options could not be selected due to reimbursement issues in Korea. Therefore, the previously reported prognostic factors were not well validated in our cohort, and the treatment outcomes were slightly inferior. This analysis of POEMS syndrome is the first for Korea, and the clinical characteristics were well-balanced with those reported from other countries.[15-17] We will be able to suggest appropriate prognostic models and personalized treatment approaches in a future study based on these experiences.

In conclusion, our study demonstrated that the demographics of Korean patients with POEMS syndrome were similar to those reported in previous studies from other countries. With the introduction of new treatment agents and the reduction of TRM rates related to ASCT, the treatment outcomes of Korean patients with POEMS syndrome have improved in recent years. However, appropriate prognostic factors for predicting treatment outcomes should be identified and validated in a large patient population. Furthermore, personalized treatment strategies, including upfront ASCT, should be applied according to risk groups and comorbidities.

ACKNOWLEDGMENTS

This study was presented in the form of a poster at the 71st annual conference of the Korean Association of Internal Medicine, Seoul, Korea, October 24–25, 2020.

MID (Medical Illustration & Design), as a member of the Medical Research Support Services of Yonsei University College of Medicine, providing excellent support with medical illustration.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Characteristics related to volume overload according to VEGF elevation

Click here to view

Supplementary Table 2

Univariate and multivariate Cox analysis for OS and PFS

Click here to view

Supplementary Table 3

First line treatment of all treated patients by diagnosis period

Click here to view

Supplementary Table 4

Univariate and multivariate logistic regression for treatment-related mortality after autologous stem cell transplantation

Click here to view

Supplementary Table 5

Univariate and multivariate Cox analysis for OS and PFS in ASCT patients

Click here to view

Supplementary Fig. 1

Overall survival (**A**) and progression-free survival (**B**) of treated patients at diagnosis.

Click here to view

Supplementary Fig. 2

Overall survival (**A**) and progression-free survival (**B**) of all treated patients according to risk groups.

Click here to view

REFERENCES

1. Watanabe O, Arimura K, Kitajima I, Osame M, Maruyama I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. *Lancet* 1996;347(9002):702.
PUBMED | CROSSREF
2. Kanai K, Kuwabara S, Misawa S, Hattori T. Failure of treatment with anti-VEGF monoclonal antibody for long-standing POEMS syndrome. *Intern Med* 2007;46(6):311-3.
PUBMED | CROSSREF
3. Samaras P, Bauer S, Stenner-Liewen F, Steiner R, Zweifel M, Renner C, et al. Treatment of POEMS syndrome with bevacizumab. *Haematologica* 2007;92(10):1438-9.
PUBMED | CROSSREF

4. D'Souza A, Hayman SR, Buadi F, Mauermann M, Lacy MQ, Gertz MA, et al. The utility of plasma vascular endothelial growth factor levels in the diagnosis and follow-up of patients with POEMS syndrome. *Blood* 2011;118(17):4663-5.
PUBMED | CROSSREF
5. Nakanishi T, Sobue I, Toyokura Y, Nishitani H, Kuroiwa Y, Satoyoshi E, et al. The Crow-Fukase syndrome: a study of 102 cases in Japan. *Neurology* 1984;34(6):712-20.
PUBMED | CROSSREF
6. Kuwabara S, Dispenzieri A, Arimura K, Misawa S, Nakaseko C. Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome. *Cochrane Database Syst Rev* 2012;2012(6):CD006828.
PUBMED | CROSSREF
7. Jang IY, Yoon DH, Kim S, Lee K, Kim KK, Lim YM, et al. Advanced POEMS syndrome treated with high-dose melphalan followed by autologous blood stem cell transplantation: a single-center experience. *Blood Res* 2014;49(1):42-8.
PUBMED | CROSSREF
8. Shim H, Seol CA, Park CJ, Cho YU, Seo EJ, Lee JH, et al. POEMS syndrome: bone marrow, laboratory, and clinical findings in 24 Korean patients. *Ann Lab Med* 2019;39(6):561-5.
PUBMED | CROSSREF
9. Dispenzieri A. POEMS syndrome: 2021 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2021;96(7):872-88.
PUBMED | CROSSREF
10. Wang C, Huang XF, Cai QQ, Cao XX, Duan MH, Cai H, et al. Prognostic study for overall survival in patients with newly diagnosed POEMS syndrome. *Leukemia* 2017;31(1):100-6.
PUBMED | CROSSREF
11. Kourelis TV, Buadi FK, Gertz MA, Lacy MQ, Kumar SK, Kapoor P, et al. Risk factors for and outcomes of patients with POEMS syndrome who experience progression after first-line treatment. *Leukemia* 2016;30(5):1079-85.
PUBMED | CROSSREF
12. D'Souza A, Lacy M, Gertz M, Kumar S, Buadi F, Hayman S, et al. Long-term outcomes after autologous stem cell transplantation for patients with POEMS syndrome (osteosclerotic myeloma): a single-center experience. *Blood* 2012;120(1):56-62.
PUBMED | CROSSREF
13. Dispenzieri A. POEMS syndrome: 2017 update on diagnosis, risk stratification, and management. *Am J Hematol* 2017;92(8):814-29.
PUBMED | CROSSREF
14. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;15(12):e538-48.
PUBMED | CROSSREF
15. Suichi T, Misawa S, Beppu M, Takahashi S, Sekiguchi Y, Shibuya K, et al. Prevalence, clinical profiles, and prognosis of POEMS syndrome in Japanese nationwide survey. *Neurology* 2019;93(10):e975-83.
PUBMED | CROSSREF
16. Keddie S, Foldes D, Caimari F, Baldeweg SE, Bomsztyk J, Ziff OJ, et al. Clinical characteristics, risk factors, and outcomes of POEMS syndrome: a longitudinal cohort study. *Neurology* 2020;95(3):e268-79.
PUBMED | CROSSREF
17. Dispenzieri A, Kyle RA, Lacy MQ, Rajkumar SV, Therneau TM, Larson DR, et al. POEMS syndrome: definitions and long-term outcome. *Blood* 2003;101(7):2496-506.
PUBMED | CROSSREF
18. Kansagra A, Dispenzieri A, Fraser R, Estrada-Merly N, Sidana S, Nishihori T, et al. Outcomes after autologous hematopoietic cell transplantation in POEMS syndrome and comparison with multiple myeloma. *Blood Adv* 2022;6(13):3991-5.
PUBMED | CROSSREF
19. Li J, Duan MH, Wang C, Huang XF, Zhang W, Cao XX, et al. Impact of pretransplant induction therapy on autologous stem cell transplantation for patients with newly diagnosed POEMS syndrome. *Leukemia* 2017;31(6):1375-81.
PUBMED | CROSSREF
20. Cook G, Iacobelli S, van Biezen A, Ziagkos D, LeBlond V, Abraham J, et al. High-dose therapy and autologous stem cell transplantation in patients with POEMS syndrome: a retrospective study of the Plasma Cell Disorder sub-committee of the Chronic Malignancy Working Party of the European Society for Blood & Marrow Transplantation. *Haematologica* 2017;102(1):160-7.
PUBMED | CROSSREF

21. Kawajiri-Manako C, Sakaida E, Ohwada C, Miyamoto T, Azuma T, Taguchi J, et al. Efficacy and long-term outcomes of autologous stem cell transplantation in POEMS syndrome: a nationwide survey in Japan. *Biol Blood Marrow Transplant* 2018;24(6):1180-6.
PUBMED | CROSSREF

22. Tomkins O, Keddie S, Lunn MP, D'Sa S. High-dose therapy and autologous transplantation for POEMS syndrome: effective, but how to optimise? *Br J Haematol* 2019;186(6):e178-81.
PUBMED | CROSSREF

23. Tokashiki T, Hashiguchi T, Arimura K, Eiraku N, Maruyama I, Osame M. Predictive value of serial platelet count and VEGF determination for the management of DIC in the Crow-Fukase (POEMS) syndrome. *Intern Med* 2003;42(12):1240-3.
PUBMED | CROSSREF

24. Kourelis TV, Dispenzieri A. Validation of a prognostic score for patients with POEMS syndrome: a mayo clinic cohort. *Leukemia* 2017;31(5):1251.
PUBMED | CROSSREF

25. Kim YR. Update on the POEMS syndrome. *Blood Res* 2022;57:27-31.
PUBMED | CROSSREF

26. Khwaja J, D'Sa S, Lunn MP, Sive J. Evidence-based medical treatment of POEMS syndrome. *Br J Haematol* 2023;200(2):128-36.
PUBMED | CROSSREF