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ARTICLE

A Retrospective Analysis of Morbidity and Risk Factors of Multiple Myeloma with Peripheral Neuropathy

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Abstract

Aims/Background Peripheral nerve injury affects some people with multiple myeloma; this condition can be brought on by the disease itself or by the treatments they receive. Such a complication increases patients' financial burden, causes treatment to be interrupted or delayed, and reduces treatment efficacy. However, opinions regarding the risk factors for peripheral neuropathy are currently divided. Consequently, the primary goals of this study were to determine the prevalence of peripheral neuropathy and related risk factors in newly diagnosed and untreated patients of multiple myeloma.

Methods Sixty-one patients with newly diagnosed and untreated multiple myeloma were retrospectively analyzed. Peripheral neuropathy (PN) in all patients was assessed via electromyography. The patients were divided into two groups according to the presence of PN. The differences in body mass index, haemoglobin, monoclonal M protein (M protein) and other related indicators between the two groups were analyzed using independent sample *t*-tests and Mann-Whitney U tests.

Results Of the 61 patients, 72% had PN. Neuroelectrophysiological studies revealed that PN patients have abnormalities in both their motor and sensory fibres. We discovered that PN was strongly correlated with age, haemoglobin, and levels of creatinine ($p = 0.039$, $p = 0.045$, and $p = 0.030$, respectively).

Conclusion Age, haemoglobin and creatinine levels are associated with the occurrence of PN. Investigation of the incidence and risk factors of multiple myeloma-associated PN can provide a better theoretical basis for the selection of treatment options and the enhancement of patient well-being and satisfaction.

Key words: multiple myeloma; peripheral neuropathy; renal insufficiency; anaemia; aged

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Introduction

Multiple myeloma (MM) is a haematological malignancy that accounts for 10% of all haematological diseases and 1% of all malignant tumours. Unfortunately, population ageing has contributed to the annual increase in its incidence (Lakshman et al, 2015).

MM is an incurable disease. However, the advent of treatments such as proteasome inhibitors, immunomodulators, CD38 monoclonal antibodies, and autologous hematopoietic stem cell transplantation has greatly improved the progression-free survival and overall survival of patients affected, with some of the cases surviving beyond 10 years. MM is associated with multiple clinical manifestations, including anaemia, hypercalcemia, bone destruction, and renal impairment, which may lead

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to fatigue, loss of appetite, dizziness, nausea, vomiting, and bone pain (Liu et al, 2023). Of note, peripheral neuropathy (PN) induced by MM can also greatly reduce patients' quality of life, presenting as sensory disturbance, pain, numbness, body temperature change, excessive sweating, reduced sweating, paralysis, muscle tone changes, muscle atrophy, etc., and such complications can pose a very significant financial burden on the patients.

Thus far, there is no data regarding the prevalence of PN induced by MM and the related risk factors. A study has shown that individuals with a body mass index (BMI) $\geq$23.7 kg/m^2 may have higher odds of developing PN, with obese patients having a higher incidence of PN (Lakshman et al, 2015). Several studies have shown that malnutrition may play a role in the development of PN, by causing hypokalemia and subsequently vitamin deficiencies prior to the precipitation of PN (Khalid et al, 2024; Kramarz et al, 2023; Lakshman et al, 2015; Lalley et al, 2024).

The present study aimed to analyze the correlation between the baseline characteristics of patients with newly diagnosed and untreated MM (including renal impairment, age, monoclonal M protein [M protein] level, and BMI) and the presence of PN, with the goal of exploring the risk factors of MM-related PN, which provides the theoretical foundation for designing treatments for this dire complication.

Methods

Patients

Patients aged $\geq$18 years, who were newly diagnosed and untreated MM and hospitalized at Hebei General Hospital between June 2021 and June 2023, were included in this study.

The diagnosis of MM was conducted according to the 2008 International Myeloma Working Group Criteria and newly diagnosed Multiple Myeloma: Understanding the Menu published in Hematology and Hematology Education in 2022. Clonal bone marrow plasma cells $\geq$10% or Biopsy-proben plasmacytoma. Hypercalcemia: Serum calcium $>$11 mg/dL or $>$1 mg/dL above upper limit of normal (ULN); Renal insufficiency: Serum creatinine $>$2 mg/dL or CrCl $<$40 mL/min; Anaemia: Haemoglobin $<$10 g/dL or $>$2 g/dL below lower limit of normal (LLN); Bone lesions: $\geq$1 osteolytic lesion (on whole-body low-dose computed tomography or positron emission tomography scan); Or $\geq$60% clonal bone marrow plasma cells; Involved to uninvolved free light chain ratio $\geq$100 and involved free light chain $\geq$10 mg/dL; $>$1 focal lesion on magnetic resonance imaging $\geq$5 mm in size (Costello, 2022). All patients had given their informed consent prior to participation. This study was approved by the ethics committee of Hebei General Hospital (2024-LW-148) and was conducted in accordance with the Declaration of Helsinki.

PN caused by other factors should be excluded to avoid affecting the prevalence statistics. Exclusion criteria of this study are as follows: (1) previous exposure to neurotoxic drugs (such as anti-tuberculosis drugs, sedatives, etc.); (2) diabetic peripheral neuropathy due to poor blood glucose control; and (3) neuralgia after herpes zoster. A retrospective study had been conducted to clarify the prevalence of

newly diagnosed MM-related PN in our hospital, and to explore the risk factors for the occurrence of MM-related peripheral neuropathy (Van den Bergh et al, 2021).

MM-related PN is mainly manifested as sensory and/or motor nerve involvement, mainly manifested as loss of pain and temperature perception, and some patients affected may experience diarrhoea or constipation. In this study, physical examination revealed decreased muscle strength or hyporeflexia of the ankle among the affected patients. Electromyography is the gold-standard diagnostic tool for PN, which features abnormal spontaneous activity of one or more nerves, including sural nerve, ulnar nerve and radial nerve. A positive electromyography test, combined with any of the clinical features, can be used to diagnose PN (Mauermann, 2017).

Clinical Testing Methods

All of the patients were evaluated for PN based on their medical history and neuroelectrophysiological examinations using electroneurography. Electromyography and nerve conduction studies were examined simultaneously to measure nerve conduction function to determine the nerve roots and nerve pathways that were injured. In the multichannel electromyograph test, the core of the concentric needle electrode was inserted into the muscle, and the unit electric potential of the motor neuron was recorded to quantify the muscle's electrical activity (Fournier and Tabti, 2019). The diagnostic criteria for peripheral nerve demyelination include latency delay of greater than 125% of the normal latency and slowing of conduction to less than 80% of normal speed.

Statistical Analysis

Continuous variables of the normal distribution are expressed as mean ± standard deviation, and independent sample *t*-tests were used to compare the differences between groups. Continuous variables with non-normal distribution are expressed as median ± interquartile range, and Mann-Whitney U tests were used to analyze the difference between groups. For all statistical tests, p values <0.05 were regarded as statistically significant. A violin plot was used to show the distribution and density of the data. The 2.5%, 25%, 50%, 75% and 97.5% quantiles were shown in the middle part of the violin plot, and the lines in the middle showed the lines connecting the minimum and maximum values. All analyses were performed using IBM SPSS Statistics version 25.0 (International Business Machines Corporation, Chicago, IL, USA).

Results

Baseline and Clinical Characteristics of Patients

The clinical data of 61 patients with newly diagnosed multiple myeloma were retrospectively analyzed. Table 1 presents the baseline and clinical characteristics of this sample, whereas Table 2 presents the comparison between the groups with and without PN.

Of the 61 patients included, 44 suffered PN, with a prevalence of 72%. Electroneurograms in most patients with PN show sensory and motor fibre involvement,

Table 1. Baseline and clinical characteristics of patients with untreated multiple myeloma.

Characteristics	Minimum	Maximum	Average value	Standard deviation
Age (years)	39	90	68	9.03
BMI (kg/m^2)	16.34	41.92	25.43	4.50
M protein (g/L)	0.00	81.00	27.40	23.58
β2-microglobulin (mg/L)	1.41	25.90	7.15	4.60
Neutrophil ($\times10^9$/L)	0.82	6.32	3.03	1.23
Leukomonocyte ($\times10^9$/L)	0.17	3.18	1.37	0.66
Haemoglobin (g/L)	42.00	147.00	84.23	20.29
Blood platelet ($\times10^9$/L)	54.00	427.00	167.85	72.43
Creatinine (μmol/L)	38.00	1238.00	197.31	223.44
Albumin (g/L)	22.00	59.00	33.50	6.97
Globulin (g/L)	12.00	129.00	54.96	31.32
LDH (IU/L)	37.00	320.00	163.37	54.69

Abbreviations: BMI, body mass index; LDH, Lactate dehydrogenase; M protein, monoclonal M protein.

mostly with reduced F waves and bilateral symmetrical reduction in the amplitude of the sural nerve sensory action potential. According to the results, the patients with PN were older than those without PN (67 vs 62 years, $p = 0.039$; Fig. 1). Patients with PN experienced more severe anaemia than those without PN (82.7 vs 92 g/L, $p = 0.045$; Fig. 2). Creatinine levels were higher in patients with PN than those without PN (215.3 vs 152.8 μmol/L, $p = 0.03$; Fig. 3). There were no significant statistical differences in BMI, β2-microglobulin level, M protein level, albumin level, globulin, neutrophil-to-lymphocyte ratio between the two groups of patients ($p > 0.05$).

Discussion

MM is a malignancy of the hematologic system and represents the second most common haematological tumour. The span of survival of patients with MM varies greatly, ranging from a few months to more than ten years. The continuous development of various therapeutic drugs such as proteasome inhibitors, immunomodulators, CD38 monoclonal antibodies, and autologous hematopoietic stem cell transplantation has contributed to a substantial improvement in the remission rate of MM (Wen et al, 2023). However, treatments with these drugs, such as proteasome inhibitors and immunomodulators, may precipitate the occurrence of peripheral nerve damage, which prompts treatment termination initiated by patients themselves. Due to the limited availability of treatment options, some patients may discontinue treatment because of the occurrence of neurological disorders. Although the incidence of PN has decreased in recent years with the introduction of subcutaneous injection for bortezomib and the development of second- and third-generation proteasome inhibitors, PN remains a dire complication faced by some patients. The combination of bortezomib, lenalidomide, and dexamethasone for the treatment of MM remains the recommended first-line treatment.

Table 2. Comparison of baseline and clinical characteristics between patients with and without PN.

Characteristics	No PN (average)	PN (average)	*p*-value	*t*/*Z* value
Age (years)	62 (10)	67 (9)	$p = 0.039^b$	–2.067
BMI (kg/m^2)	23 (6)	25.3 (6)	$p = 0.238^b$	–1.181
M protein (g/L)	12.9 (46)	26.6 (45)	$p = 0.380^b$	–0.877
β2-microglobulin	5.70 (8)	6.15 (5.6)	$p = 0.445^b$	–0.764
Neutrophil-to-lymphocyte ratio	1.9 (3.6)	2 (2.3)	$p = 0.910^b$	–0.113
Haemoglobin (g/L)	92 ± 23	82.7 ± 19	$p = 0.045^a$	2.030
Blood platelet	151 (95)	167 (87)	$p = 0.520^b$	–0.644
Creatinine (μmol/L)	152.8 (100)	215.3 (187)	$p = 0.030^b$	–0.213
Albumin (g/L)	33.6 (9)	32.3 (10)	$p = 0.274^b$	1.094
Globulin (g/L)	47.9 ± 9	57.7 ± 32	$p = 0.278^a$	–1.096
LDH (IU/L)	150.7 ± 48	168.3 ± 56	$p = 0.263^a$	–1.131

Notes: [a] Analyzed with independent samples *t*-test; [b] Analyzed with Mann-Whitney U test. Normally distributed variables like haemoglobin, globulin and LDH are expressed as mean ± standard deviation. Variables with non-normal distribution like age, BMI, M protein, β2-microglobulin, neutrophil-to-lymphocyte ratio, blood platelet, albumin, and creatinine are expressed as median (interquartile range).

Abbreviations: BMI, body mass index; LDH, Lactate dehydrogenase; M protein, monoclonal M protein; PN, peripheral neuropathy.

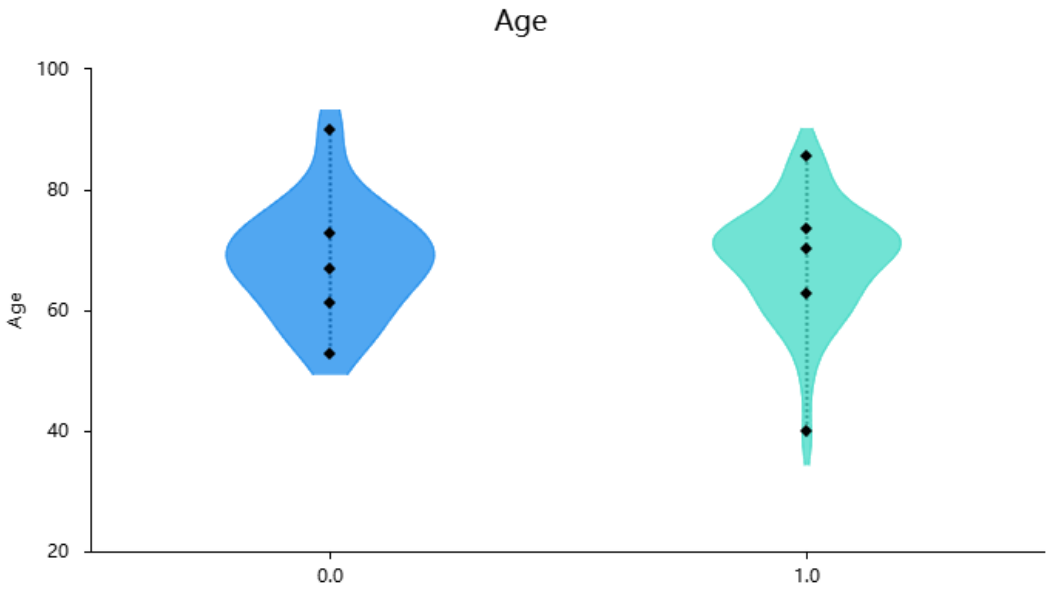

Fig. 1. Violin plot depicting age difference between patients with and without peripheral neuropathy (PN). The blue colour represents patients without PN, and the green colour represents patients with PN.

PN is a common neurological complication of MM that features numbness, tingling, and neuropathic pain. It seriously affects the comfort of patients' lives and has adverse effects, resulting in a decline in the executive ability of cancer

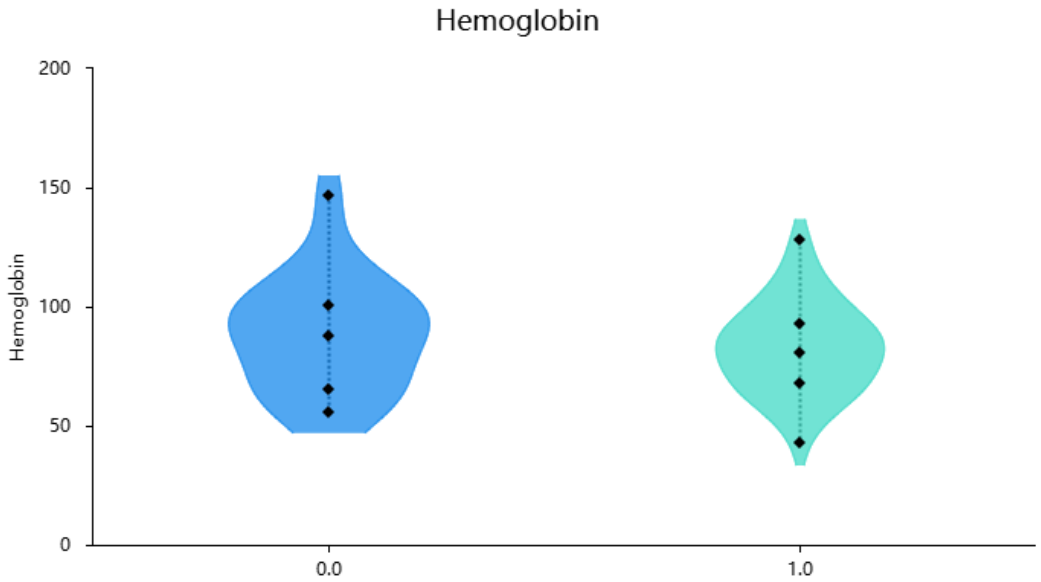

Fig. 2. Violin plot depicting haemoglobin level difference between patients with and without peripheral neuropathy (PN). The blue colour represents patients without PN, and the green colour represents patients with PN.

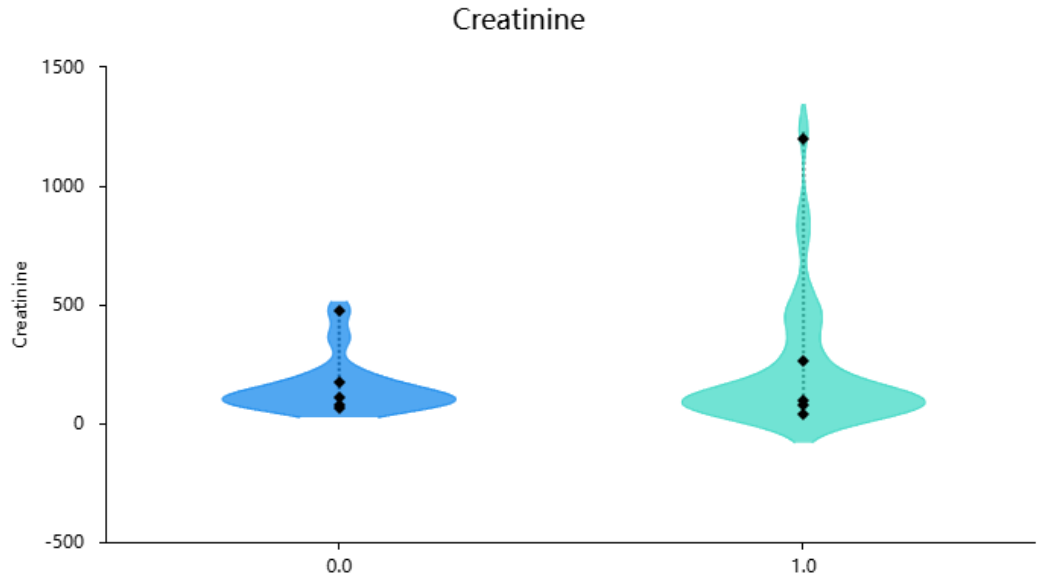

Fig. 3. Violin plot depicting creatinine level difference between patients with and without peripheral neuropathy (PN). The blue colour represents patients without PN, and the green colour represents patients with PN.

survivors and loss of happiness in life (Jheng et al, 2024; McNeish et al, 2024; Moreno-Alonso et al, 2024). MM-associated PN is mainly a form of demyelinating neuropathy caused by immunoglobulin deposition into axons and, to a lesser extent, light-chain amyloid deposition. Nahi et al (2021) study suggested that frequent visit to the hospital is a contributing factor to pain in patients, as evidenced by the fact that patients with PN visit outpatient clinics more often than those without PN, and patients with PN tend to stay longer in the hospital. PN also increases the economic burden on patients with PN, as shown by the significantly higher annual outpatient

costs incurred from PN treatment when compared with treatment costs for patients without PN (52,352 vs 31,194 euros) (Nahi et al, 2021). Therefore, studying the incidence and related risk factors of PN related to MM and controlling these risk factors may contribute to a general relief of pain experienced by the patients and diminish the economic burden on those with PN.

The analysis of this study suggests that about 70% of MM patients have PN at the initial diagnosis. This finding far exceeds the 7.2% reported in an Italian study (Leone et al, 2016) but is close to the incidence of PN in newly diagnosed MM of 62.1% reported in an Indian study (Malhotra et al, 2011).

As expected, we found that age was associated with the development of PN; the older the age, the higher the probability of PN development. The results were similar to those of other studies (Jhana and Shuba, 2023; Wildes et al, 2019). Our research showed that patients with PN had higher creatinine levels, indicating that the occurrence and development of PN are related to renal dysfunction. This result is consistent with that of Kitala-Tańska et al (2024), who reported that nerve pain is very common in patients with chronic kidney disease. They reported that 47.5% of patients with chronic kidney disease had chronic pain, including PN (Kitala-Tańska et al, 2024). The prevalence of PN among patients with renal insufficiency is multifaceted, with uremia and hyperkalemia cited as factors leading to peripheral nerve damage in the context of renal dysfunction. Studies have shown that magnesium plays a vital role in chronic pain. Magnesium may be beneficial in reducing the frequency and severity of peripheral neuropathy symptoms in patients with chronic kidney disease, indicating that in patients with MM and renal dysfunction, the use of transdermal magnesium may reduce the occurrence of PN and relieve pain (Athavale et al, 2023; Engen et al, 2015).

In this study, we found that patients with nerve damage had lower haemoglobin levels, indicating that anaemia is related to the occurrence of peripheral nerve damage; this reflects that the severity of anaemia is tied to the likelihood of PN development. This finding is consistent with the results reported by Jhana and Shuba (2023), who found that the amplitudes of the median and sural nerves were significantly reduced in patients with diabetic PN combined with anaemia. In fact, it has been speculated that improving anaemia may reduce the incidence of PN. Some studies have suggested that the neutrophil-to-lymphocyte ratio is related to the probability of developing diabetic PN; the higher the ratio, the higher the probability of developing PN (Chen et al, 2021; Demirdal and Sen, 2018; Liu et al, 2017). However, the results of this study showed that the neutrophil-to-lymphocyte ratio was not significantly associated with the occurrence of PN, which is inconsistent with the reported findings and speculations. This may also indicate that diabetic PN and MM-related PN arise from different pathogenetic pathways. In addition, it has been suggested that BMI may be related to sensory PN (Lakshman et al, 2015), although BMI was not correlated with the occurrence of PN.

The current study is not without limitations. This retrospective study employed a small sample, and certain data were missing, potentially leading to results bias. In addition, no correlation analysis was performed in this study, and the results may

not be accurate due to the influence of confounding factors. Future studies should employ a larger sample size and multicenter data to validate the results of this study.

Conclusion

In conclusion, age, renal function status, and degree of anaemia are associated with the incidence of PN. Given that age is a nonmodifiable factor, the control and mitigation efforts of PN should focus on modifying renal function and ameliorating anaemia.

Key Points

- Peripheral nerve injury affects some people with multiple myeloma.
- Peripheral nerve injury was associated with 72% of newly diagnosed multiple myeloma.
- Advanced age, renal impairment and anaemia are associated with the occurrence of peripheral neuropathy in multiple myeloma, but further confirmation with larger samples is needed.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

XHG and JL contributed to the design and implementation of the research. YJL, YTL and YYW contributed to the analysis of the results. JY and YL conceived the original and supervised the project. XHG and JL drafted the manuscript. All authors have contributed to the writing of the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All patients had given their informed consent prior to participation. This study was approved by the ethics committee of Hebei General Hospital (2024-LW-148) and was conducted in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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