International Journal of General Medicine

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ORIGINAL RESEARCH

Clinical Characteristics and Risk Factors for Pleural Effusion in Patients with Multiple Myeloma

This article was published in the following Dove Press journal:
International Journal of General Medicine

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Purpose: Pleural effusion (PE) is prevalent in "real-life" populations of multiple myeloma (MM), a common hematologic malignancy. Development of PE likely has prognostic implications. The aim of this study was to investigate the characteristics and identify risk factors for occurrence of PE in MM.

Patients and Methods: We reviewed electronic medical records of 907 patients diagnosed with MM.

Results: Incidence of PE in MM patients was 42.7%. Small and bilateral PE in most cases. PE developed in all MM subtypes, the median time from diagnosis of multiple myeloma to pleural effusion was 6.8 months (range 0.8–33.6 months). Patients with PE showed worse survival than those without PE (unadjusted hazard ratio with 95% confidence interval: 2.249 [1.774–2.852]). No difference in survival was found between patients with small PE and those with moderate to large PE (unadjusted HR, 1.402; 95% CI, 1.037–1.896). Plasma cell proportion (OR, 1.373; 95% CI, 1.153–1.634; P = 0.009) and amyloidosis (OR, 1.791; 95% CI, 1.408–2.279; P = 0.024) were risk factors for the occurrence of PE at the initial diagnosis of MM. Plasma cell proportion (OR, 1.853; 95% CI, 1.451–2.368; P = 0.038), pneumonia (OR, 1.309; 95% CI, 1.143–1.498; P = 0.008) and heart failure (OR, 1.815; 95% CI, 1.387–2.374; P = 0.031) were risk factors for the occurrence of PE at relapse of MM.

Conclusion: The incidence of PE in MM patients is notable and PE can occur in all MM subtypes. PE indicates a poor prognosis, even small amounts of effusion. PE is a problem worthy of attention, especially in patients with high plasma cell proportion, amyloidosis or complicated with pneumonia and heart failure.

Keywords: pleural effusion, multiple myeloma, incidence, risk factors, overall survival

Introduction

Pleural effusion (PE) is a common clinical problem. It is estimated that about 1.5 million people suffer from PE in the United States.[1] PE can be caused by a variety of reasons, including disease local to the pleura or systemic condition.[2–4] Hematologic malignances are one of the causes of pleural effusion. Appearance of PE portends a poorer prognosis in cancer patients.[5,6] It was reported that appearance of PE is associated with clinical response during hematologic malignances treatment.[7,8] Evaluation of pleural effusion in patients with hematologic malignances is required.

Multiple myeloma (MM) is the second most frequent hematologic malignancy, and each year over 30,000 new cases are diagnosed in the USA.[9,10] In Asian countries, the incidence of MM has increased rapidly during the past two decades, and MM now represents the third most common hematologic disease in South Korea.[11,12] It is estimated that incidence of MM patients in China was 27,800 new cases each year

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http://doi.org/10.2147/IJGM.S300337

and a total of 200 000 cases in China.[13] Multiple myeloma is a clonal B-cell malignancy characterized by proliferation of uncontrolled plasma cells in the bone marrow or extramedullary sites, leading to excessive production of immunoglobulins. Anemia, renal failure, hypercalcemia, and lytic bone lesions are the most commonly encountered manifestations of MM.[14]

In our center, PE is frequently diagnosed in patients with MM. Previous literature reported the PE frequency of 10.7% to 13.9%.[15,16] However, according to our observations, the incidence of PE in MM patients is much higher. Hitherto, articles on PE in MM patients were mostly case reports, comprehensive studies of PE in MM patients have not been performed. There is a pressing need to better understand the clinical characteristics and risk factors for PE in patients with MM. Thus, here we aimed to investigate the incidence, distribution, and outcomes of PE in patients with MM, and to investigate risk factors for PE in MM patients.

Patients and Methods

Study Population and Data Collection

This was a retrospective, single-center study. We identified a total of the 907 patients who were diagnosed with multiple myeloma were admitted to Beijing Chao-yang Hospital between January 01, 2000, and December 31, 2017. There were 46 patients without computed tomography (CT) of the chest, which were excluded from the study. Among the enrolled 861 MM patients, 528 (61.3%) were newly diagnosed, and 208 (24.2%) were relapsed multiple myeloma (Figure 1).

The detailed medical history, clinical presentation, laboratory results, and imaging data from all patients were extracted from the electronic medical records. We studied various aspects of PE associated with MM. The study protocol was approved by the Institutional Review Board for Human Studies of Beijing Chaoyang Hospital, Beijing, China. The study was carried out in conformity to the Declaration of Helsinki. The review board exempted the acquisition of informed consent because this was a retrospective study. Patients' data confidentiality was fully respected during data collection and the preparation of the manuscript.

Diagnosis and Evaluations

The International Myeloma Working Group (IMWG) criteria for the diagnosis of MM were adopted. The survival of all enrolled patients was followed up to December 31, 2018, or until death. Patients were categorized according to the Durie-Salmon staging system (DS) and the International Staging System (ISS).[17,18] Definition of relapsed multiple myeloma based on the International Myeloma Working Group relapse criteria for multiple myeloma.[19,20]

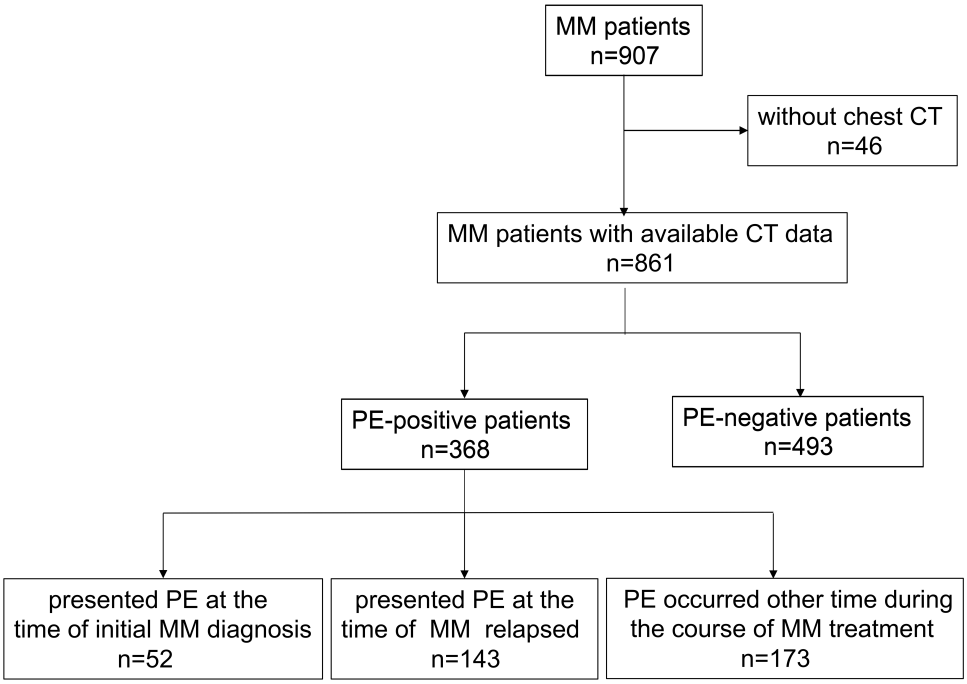

Figure 1 Flow chart of study population.
Abbreviations: MM, multiple myeloma; PE, pleural effusion; CT, computed tomography.

Chest CT was performed to evaluate PE. In our center, the chest CT scans were routinely examined when the patients were initially admitted, and were performed before new course of chemotherapy, or when fever, cough, expectoration, dyspnea, and other respiratory symptoms appeared, as determined by two hematologists and pulmonologists. Malignant pleural effusions (MPE), which are diagnosed based on malignant cells in the pleura or the pleural fluid.

The size of effusion was evaluated on CT scans according to the CT imaging features with anteroposterior quartile and maximum anteroposterior depth measured at the midclavicular line as described by Moy et al. The first anteroposterior-quartile effusions were small, second quartile effusions were moderate, and third and fourth quartile effusions were large.[21] Evaluation of PE was done by radiologists and pulmonologists. For statistical considerations, data were analyzed based on the first identified PE in each patient.

Statistical Analysis

Categorical variables were described using counts and percentages, and groups were compared using a chi-square test or Fisher's exact probability test. Continuous variables were presented as means and standard deviations, and significant differences between two groups were determined with a Student's *t*-test. For non-normally distributed data, median and interquartile ranges were used to describe the features, while comparisons of the two sets were performed using a Mann–Whitney *U*-test. Survival rate was calculated using the Kaplan–Meier (KM) method. The median duration of the follow-up and its 95% CI were calculated using the reverse KM method. To determine the factors associated with the occurrence of pleural effusion in MM, logistic regression analysis was performed. The odds ratios (OR) with 95% confidence intervals (CI) were presented. The statistical analysis of data was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and R software (version 3.5.1) with the corresponding R packages. All tests were two-sided, and a value of $P < 0.05$ was considered statistically significant.

Results

Incidence and Distribution of Pleural Effusion in Multiple Myeloma Patients

A total of 368 patients had pleural effusion occurred during the course of treatment of MM identified on CT out of 861 patients with available CT data, yielding the incidence of 42.74%. The median follow-up time of the study population was 44.9 months (95% CI, 42.6–48.8). Characteristics of patients with and without pleural effusion are summarized in Table 1. There were no significant differences in age, sex, myeloma subtypes, and staging distribution between 861 included patients with available CT data and 46 patients without chest CT data (Supplementary Table 1).

The median time from diagnosis of multiple myeloma to pleural effusion was 6.8 months (range 0.8–33.6 months), 56.3% patients developed PE in the first year following the initial diagnosis of MM. PE developed in all myeloma subtypes, the distribution of myeloma types in patients with PE was similar to patients without PE. While 321 (87.2%) patients developed PE presented with DS stage III, 213 (57.9%) patients presented with ISS stage III. The distribution of myeloma staging using the DS and ISS was significantly different between the PE-negative and PE-positive group ($P = 0.015$, $P < 0.001$, respectively). The characteristics of patients developed PE are shown in Table 1.

The distribution features of pleural effusion in multiple myeloma patients are shown in Figure 2. 15.5% of PEs were left-sided, 21.5% were right-sided, while both sides were affected in 63.0% of cases. In either unilateral or bilateral effusion, 82.6% of PEs were of small size, while moderate and large sizes were present in 13.0% and 4.3% of cases, respectively. Thirteen (38.2%) malignant pleural effusions (MPE) was confirmed in 34 patients who had undergone thoracentesis, 7 (53.8%) MPE was of small size. Pneumonia and pleural hypertrophy were frequently seen in patients with PE.

Outcomes of Pleural Effusion and Overall Survival

During the median follow-up period of 44.9 months (95% CI, 42.6–48.8), the complete disappearance of PE was observed in 23 (6.25%) of the patients. Decreased PE was noted in 39 (10.6%) patients, including PE decreased then reoccurred in 9 patients. PE persisted in 138 (37.5%) patients, while PE increased in 69 (18.8%) patients. The response was not documented in the remaining 99 patients. In this study, 78/368 (19.8%) patients with PE experienced dyspnea.

Thirty-four (9.24%) patients underwent thoracentesis, 15 (44.1%) patients underwent thoracentesis because of intolerable dyspnea. The median time from the initial PE

Table 1 Characteristics of Patients with Multiple Myeloma

Variables	Total Patients (n=861)	PE-Positive Group (n=368)	PE-Negative Group (n=493)	*P* value*
Age, years	59 (52–66)	60 (54–68)	58 (51–65)	0.002
Male, No. (%)	497 (57.7)	226 (61.4)	271 (55.0)	0.068
CCI	3 (2–4)	3 (2–5)	3 (2–4)	<0.001
Monoclonal protein type, n (%)				0.957
IgG	412 (47.9)	176 (47.8)	236 (47.9)	
IgA	172 (20.0)	75 (20.4)	97 (19.7)	
IgD	58 (6.7)	27 (7.3)	31 (6.3)	
Light chain	189 (22.0)	78 (21.2)	111 (22.5)	
Others	30 (3.5)	12 (3.3)	18 (3.7)	
DS stage, n (%)				0.015
I	32 (3.7)	12 (3.3)	20 (4.1)	
IIA	79 (9.2)	30 (8.2)	49 (9.9)	
IIB	13 (1.5)	5 (1.4)	8 (1.6)	
IIIA	575 (66.8)	232 (63.0)	343 (69.6)	
IIIB	162 (18.8)	89 (24.2)	73 (14.8)	
ISS stage, n (%)				<0.001
I	139 (16.1)	44 (12.0)	95 (19.3)	
II	305 (35.4)	111 (30.2)	194 (39.3)	
III	417 (48.4)	213 (57.9)	204 (41.4)	
Del(17p)				0.349
No	541 (62.8)	228 (62.0)	313 (63.5)	
Yes	60 (7.0)	31 (8.4)	29 (5.9)	
Unknown	260 (30.2)	109 (29.6)	151 (30.6)	
Gain(1q21)				0.911
No	358 (41.6)	156 (42.4)	202 (41.0)	
Yes	243 (28.2)	103 (28.0)	140 (28.3)	
Unknown	260 (30.1)	109 (29.6)	151 (30.6)	
t(4;14)				0.343
No	515 (59.8)	228 (62)	287 (58.2)	
Yes	86 (10.0)	31 (8.4)	55 (11.2)	
Unknown	260 (30.2)	109 (29.6)	151 (30.6)	
t(14;16)				0.929
No	579 (67.2)	250 (67.9)	329 (66.7)	
Yes	22 (2.6)	9 (2.4)	13 (2.6)	
Unknown	260 (30.2)	109 (29.6)	151 (30.6)	
t(11;14)				0.929
No	513 (59.6)	222 (60.3)	291 (59.0)	
Yes	88 (10.2)	37 (10.1)	51 (10.3)	
Unknown	260 (30.2)	109 (29.6)	151 (30.6)	

Notes: Data are presented as median (interquartile range) or %. *For comparisons between PE-negative group and PE-positive group.
Abbreviations: PE, pleural effusion; CCI, Charlson Comorbidity Index; DS, Durie-Salmon; ISS, International Scoring System.

was found to the first thoracentesis was 1.0 months (range, 0–7.5 months).

One hundred and eighty-four (32.1%) patients died during the follow-up duration. The median overall survival (OS) was 82.4 months (95% CI, 72.5–89.6), and the 5-year OS rates were 62.0% (95% CI, 56.9%-67.5%). Kaplan–Meier (KM) curves of overall survival in MM patients following the initial diagnosis of MM are showed in

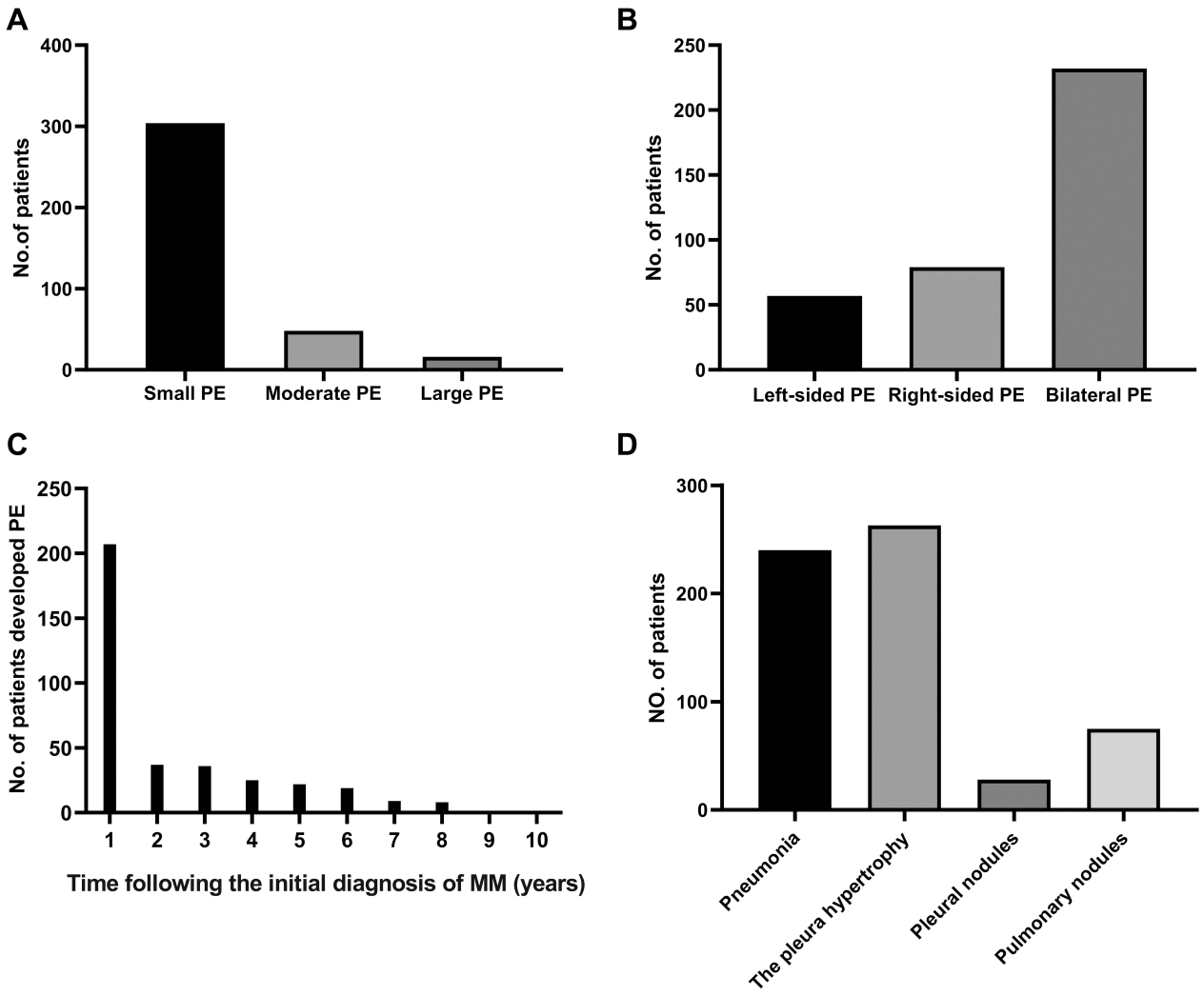

Figure 2 The distribution features of pleural effusion in multiple myeloma patients (n=368). (**A**) The effusion size distributions; (**B**) location of PE; (**C**) the occurrence time of PE; (**D**) other pulmonary CT findings.
Abbreviations: MM, multiple myeloma; PE, pleural effusion; CT, computed tomography.

Figure 3. Patients with PE showed significantly worse survival since the initial diagnosis of MM than those without PE (unadjusted HR, 2.249; 95% CI, 1.774–2.852). No difference in survival was found between patients with small PE and those with moderate to large PE (unadjusted HR, 1.402; 95% CI, 1.037–1.896).

Risk Factors for Pleural Effusion in Multiple Myeloma Patients

We explored the risk factors for pleural effusion using logistic regression, as shown in Table 2. Our study investigated patients who presented pleural effusion at the time of initial MM diagnosis or at the time of relapse. Fifty-two (9.8%) presented pleural effusion at the time of initial MM diagnosis among 528 patients who were newly diagnosed in our center. Among the 208 patients who were relapsed, 143 (68.8%) presented pleural effusion at the time of relapse. Input variables for logistic regression analysis were selected from significant variables obtained from the univariate analysis and variables related to the occurrence of PE that were reported in the previous literature, the final model contains 13 variables.

Clonal plasma cell proportion in the bone marrow at the time of initial MM diagnosis (OR, 1.373; 95% CI, 1.153–1.634; P = 0.009) and amyloidosis (OR, 1.791; 95% CI, 1.408–2.279; P = 0.024) were independent risk factors for the occurrence of pleural effusion at the initial diagnosis of MM. Clonal plasma cell proportion in the bone marrow at the time of MM relapse (OR, 1.853; 95% CI, 1.451–2.368; P = 0.038), pneumonia (OR, 1.309; 95% CI, 1.143–1.498; P = 0.008) and heart failure

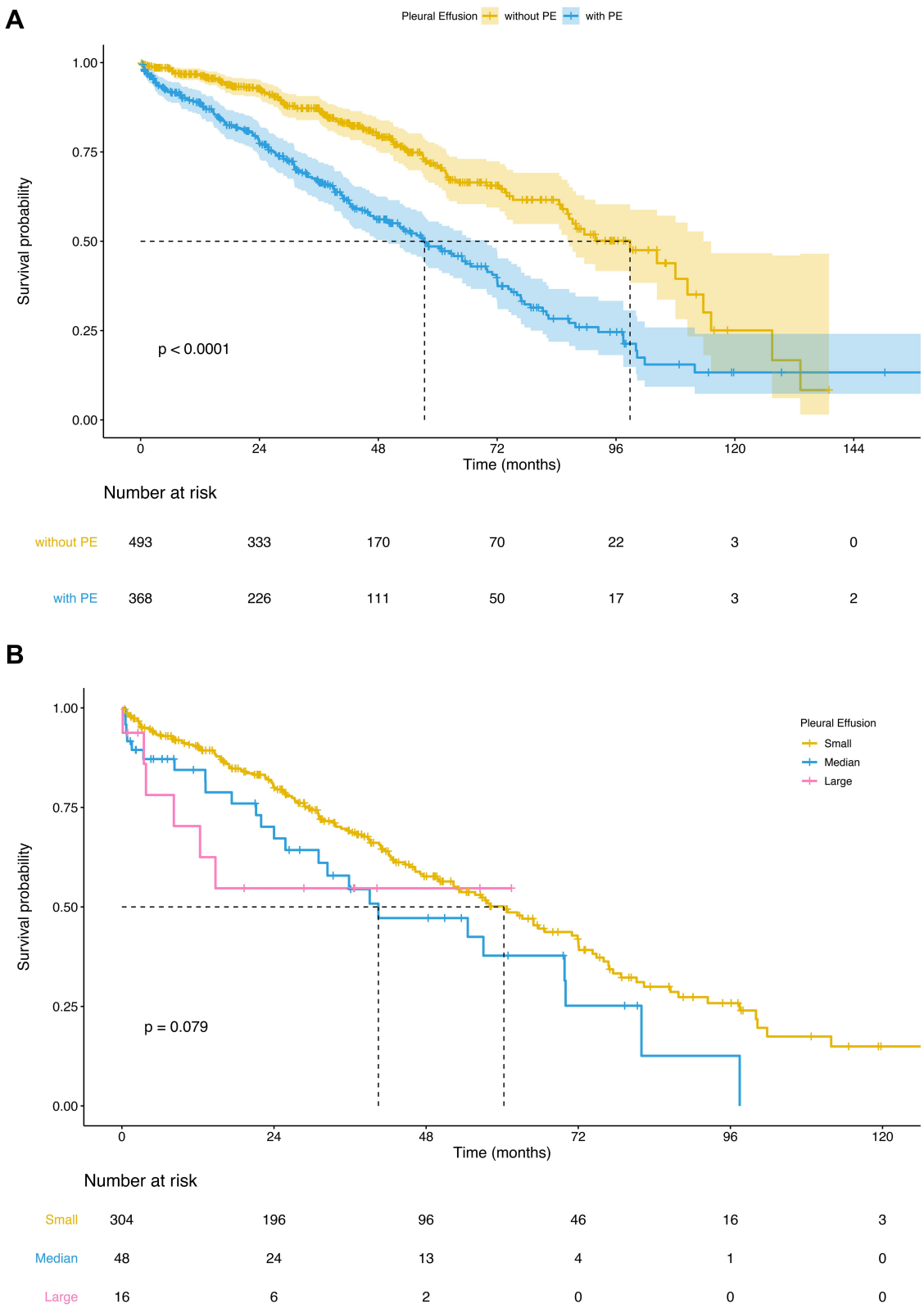

Figure 3 Kaplan–Meier (KM) curves of overall survival in MM patients following the initial diagnosis of MM. (**A**) Curves between patients with PE and patients without PE; (**B**) curves between patients with small PE and those with moderate to large PE.
Abbreviations: MM, multiple myeloma; PE, pleural effusion.

Table 2 Risk Factors for the Occurrence of Pleural Effusion in MM Patients*

Characteristics	OR (95% CI)	P value
Newly diagnosed patients		
Plasma cell proportion (>38.5% vs ≤38.5%)	1.373 (1.153–1.634)	0.009
Amyloidosis	1.791 (1.408–2.279)	0.024
Patients with relapse		
Plasma cell proportion (>38.5% vs ≤38.5%)	1.853 (1.451–2.368)	0.038
Pneumonia	1.309 (1.143–1.498)	0.008
Presence of heart failure	1.815 (1.387–2.374)	0.031

Notes: *Variables in the logistic regression that did not have a significant independent association with the occurrence of pleural effusion in multiple myeloma patients: Age, Male, M-protein types, the International Staging System (ISS) stage, Durie-Salmon staging system (DS), Fluorescence in situ hybridization (FISH) test: del(17), gain(1q21), t (4;14), t(14;16) and t(11;14), Presence of renal failure, History of tuberculous, Hypoproteinemia.
Abbreviations: MM, multiple myeloma; OR, odds ratio; CI, confidence interval.

(OR, 1.815; 95% CI, 1.387–2.374; P = 0.031) were independent risk factors for the occurrence of pleural effusion at relapse of MM.

Discussion

To the best of our knowledge, this was the largest series dealing with PE in patients with MM. The noteworthy finding in this study was the incidence of PE in MM patients. Namely, the incidence of PE in MM patients was 42.7%, which is much higher than the data from prior reports. Lower incidence in other studies may reflect the fact that most previous studies were in the form of case reports, and only two studies mentioned the frequency of PE in the range between 10.7% and 13.9%;[15,16] however, there were no detailed evaluations. Moreover, a higher incidence of PE in our series may be due to the meticulous attention paid to detecting PE in our hospital. Beijing Chao-Yang Hospital not only has the Beijing Institute of Respiratory Diseases, well recognized at the national level, but also houses one of the largest myeloma treatment centers in China. Our study suggested that the incidence of PE in MM patients is actually notable, and it is likely that MM is often overlooked in patients with PE in other centers.

We noted that patients with PE showed worse survival than those without PE. The statistical calculation is hinging on the presence or absence of pleural effusion, whatever the clearly etiologies of PEs. It is just the presence of PE has an impact on prognosis, which is why it is very important to identify it. Pleural effusion is almost always a manifestation of one or more underlying primary conditions. It is possible that presence of effusion is a marker of poor prognosis by virtue of the severe tumor burden or worse host comorbidity status.

Hitherto, the distribution of the PE in MM patients has not been studied. Previous studies reported inconsistent and unclear data on incidence of PE among different subtypes of MM. A higher prevalence of IgG and IgA subtypes was reported in previous case reports.[22–25] Here we found that PE occurred in all classes of myeloma subtypes. We noted that majority of PEs in our study were of small size. It is noteworthy that even small PE, its presence is an important prognostic factor of worse survival. No difference in survival was found between patients with small PE and those with moderate to large PE. In addition, MPE is not always massive, given that we found that in more than 50% MPEs was confirmed in 34 patients who had undergone thoracentesis in our study were of small size. Small PE might represent an early phase of malignant PE or severe comorbid disease. We suggested that more attention should be paid to pleural effusion, even small amounts of pleural effusion.

Another important aspect of our study was related to identification of risk factors associated with the occurrence of PE. Through logistic regression analysis, we demonstrated that plasma cell proportion was an independent risk factor for the occurrence of PE either at the initial diagnosis of MM or at the time of MM relapse. This association remained significant after adjustment for age, sex, M-protein types, the ISS or DS stage, fluorescence in situ hybridization (FISH) test, presence of heart disease or renal failure, history of tuberculous and hypoproteinemia. MM is a malignancy of the B-cell lineage, characterized by the accumulation of clonal plasma cells in the bone marrow, leading to excessive production of immunoglobulins. High proportion of clonal plasma cells in the bone marrow indicates greater severity of the disease.[26,27] It is supposed that a factor of the development of PE in MM

patient is the production of large quantities of immunoglobulins, which leads to high colloid osmotic pressure of the fluid.[28]

Additionally, in this study, amyloidosis was found to be an independent risk factor for the occurrence of PE at the initial diagnosis of MM. In amyloidosis, amyloid protein is derived from immunoglobulin light chains, and most often involves the kidneys and the heart. Direct pleural amyloidosis can also lead to pleural effusions. Sunny et al reported a case of exudate and amyloidosis in thoracoscopic pleural biopsy.[29] Pneumonia and heart failure were found to be significant independent predictors for the occurrence of pleural effusion at relapse by logistic regression. In our study, more than 65% of patients experienced pneumonia at the onset of pleural effusion in our study. For these MM patients undergoing chemotherapy, infection does play a role in the development of PE. In addition, many of MM patients have heart failure. The capillary hydrostatic pressure might be increased lead to the occurrence of PE. Multiple myeloma can have direct and indirect detrimental effects on cardiac function. Several drug classes used in the treatment of MM are known to increase the risk of cardiac events, such as doxorubicin, anthracycline, lenalidomide, pomalidomide, carfilzomib and bortezomib.[30]

Since the incidence of PE was higher than expected, these patients with PE actually pose a diagnostic and therapeutic challenge in need of better management approaches. Infection and heart failure are important factors leading to PE.[16,31] Also, considering the high prevalence of tuberculosis in China, tuberculosis might have been overlooked in these MM patients with PE. These are possibly treatable causes. On the other hand, in patients underwent thoracentesis, MPE was confirmed in13/34 (38.2%) patients. Previous literature reported the MPE in MM patients frequency of 0.8% to 2.65%.[32–34] A part of the effusions in 334 patients who did not receive additional evaluation to determine the cause of PE may be MPE, but they were not identified. Complete disappearance of PE was observed in only 6.5% patients, and most PE persisted or increased in the remaining patients. If PE went undetected or did not be pay attention to, it may result in some patients end up receiving suboptimal treatment. Identify reversible causes of PE or MPE conducive to clinical decision making. In addition, recent evidence suggests that indwelling pleural catheters are safe in hematologic malignancies.[35] Therefore, a diagnostic thoracentesis or further evaluation of PE should be performed widely in MM patients.

Though our investigation provided first comprehensive study to evaluate epidemiology, clinical characteristics, risk factors, and prognosis of PE in MM patients, it had a few limitations. First of all, our study was a real-world, single-center, retrospective cohort study, which resulted in incomplete data and inability to control examinations and treatment. Some patients were asymptomatic and may not have been picked up in the absence of routine evaluation. Long follow-up is often associated with missing data, and is likely to have bias errors. Second, few patients underwent thoracentesis, which might have limited the interpretative power on the cause of the effusion. Finally, future research will be required to determine if PE is a sign for therapy change and if more aggressive therapy after the diagnosis of PE can improve prognosis.

Conclusions

The incidence of PE in MM patients is notable and PE can occur in all MM subtypes. PE indicates a poor prognosis, even small amounts of effusion. PE is a problem worthy of attention, especially in patients with high plasma cell proportion, amyloidosis or complicated with pneumonia and heart failure.

Acknowledgments

The authors thank the patients, their families, and all investigators who participated in the study.

Disclosure

The authors report no conflicts of interest in this work.

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