

Clinicopathological Characteristics of Chinese Patients with Multiple Myeloma with Pleural Effusion: A Large Cohort Study

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Abstract

Background: Multiple myeloma (MM) is a hematologic malignancy of plasma cell origin. Multiple myeloma with pleural effusion (PE) is not uncommon. The existing literature on MM with PE in China and abroad is limited to case reports. Thus, it is necessary to investigate the characteristics of MM with PE and the associated prognosis to achieve early recognition and treatment.

Method: Patients diagnosed with MM from January 2000 to December 2019 at Peking University Third Hospitals were assessed retrospectively. We summarized and analyzed the clinical manifestations, laboratory examinations, diagnosis and prognoses of patients by using clinical data and a literature review.

Result: A total of 490 patients with MM were included. 272 patients (55.5%) had PE. Confirmed by pathology, there were 45 myelomatous pleural effusion (MPE) patients and 28 non-MPE patients. The total protein, albumin, calcium and complement C3 levels were lower and the β 2-MG levels were higher in the PE group than in the non-PE group ($P < 0.05$). Low total protein and low albumin levels were independent risk factors for PE. The levels of nucleated cells, total protein, LDH, and ADA were higher in the MPE group than the non-MPE group ($P < 0.05$). There were no significant differences in the specific gravity or the levels of protein, glucose and CEA. Multivariate regression analysis suggested that low LDH levels and high levels of nucleated cell counts, total protein and ADA in PE were independent risk factors for MPE.

Conclusions: PE is a complication of MM, and it is likely to be malignant. Low serum total protein and albumin levels are independent risk factors for MM with PE. Hypocomplement C3emia (activation of the complement bypass pathway) may affect the formation of PE in patients with MM. High nucleated cell counts, total protein and ADA levels as well as low LDH levels in PE were independent risk factors for MPE.

Background

Multiple myeloma (MM) is a malignant disease, in which clonal plasma cells proliferate abnormally. These plasma cell clones proliferate in the bone marrow and cause bone damage, which is also an important sign of MM [1]. MM is the second most common malignant tumor in the hematologic system in many countries and it is more common in the elderly population and is still incurable. Complications related to the disease include hypercalcemia, renal insufficiency, anemia and infections [1]. Pleural effusion (PE) may be a sign of thoracic involvement and was observed in approximately 6% of MM patients [2, 3]. Myelomatous pleural effusion (MPE) is particularly rare in patients with MM (< 1%), especially in patients with PE as the initial symptom [4].

The existing literature on MM with PE in China and abroad is limited to case reports. Thus, it is necessary to investigate the characteristics of MM with PE and the associated prognosis to achieve early

recognition and treatment. Therefore, this study reviewed the data of MM patients diagnosed at Peking University Third Hospitals to provide evidence for future clinical diagnosis and treatment.

Methods

Patient selection

Patients who met the following inclusion criteria were included in the study: age > 18 years patients diagnosed with MM and receiving follow-up treatment. The MM diagnostic standards were those in "Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" [5]. Figure 1 shows the screening process for MM patients with MPE.

Research methods

This study was a retrospective study. Patient demographics, clinical and laboratory data were recorded. Patients were grouped according to whether they had PE and whether the PE was benign or malignant. The Durie-Salmon (D-S) stage of MM patients was recorded at the time of diagnosis. MM was typed according to the monoclonal antibody secreted by the myeloma cells. The diagnosis of PE was based on chest radiographs, chest CT, and thoracic ultrasound. The diagnosis of MPE was based on pleural effusion cytology, pleural biopsy, and/or pleural effusion flow cytometry. The fasting venous blood and morning urine test results were recorded after diagnosis and before the administration of treatment. The abnormal levels of indicators were identified based on the reference intervals provided by the laboratory when the sample was submitted for inspection.

The levels of C-reactive protein (CRP), albumin, serum creatinine, and lactate dehydrogenase (LDH) were respectively detected with the immunoturbidimetric method, bromocresol green method, picric acid method, and the enzymatic rate method. The rate scatter turbidimetry method was used for β 2-MG, complement C3, and C4.

Statistical methods

SPSS 16.0 statistical software was used for data analysis. Measurement data that conformed to a normal distribution are expressed as the means \pm standard deviations ($\bar{x} \pm s$), and comparisons between the two groups were performed using t tests. Data that did not conform to a normal distribution are represented as the median (M(Q)), and Nonparametric tests (rank sum tests) were used for comparisons between the two groups. Count data are expressed as rates, and the χ^2 test was used for comparisons between groups. Multivariate analysis was performed using multiple logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

General data of patients with multiple myeloma and myelomatous pleural effusion

A total of 490 patients with MM were included in the study, with an average age of 60.99 ± 11.52 years; there were 297 males (60.6%) and 193 females (39.4%). According to D-S staging, there were 33 cases (6.73%) of stage IA, 8 cases (1.63%) of stage IB, 42 cases (8.6%) of stage IIA, 20 cases (4.1%) of stage IIB, 187 cases (38.2%) of stage IIIA, 193 cases (39.4%) of stage IIIB, and 7 cases (1.4%) of an unknown stage. In terms of typing, 88 cases were IgA (18.0%), 15 cases were IgD (3.1%), 139 cases were IgG (28.4%), 130 cases were other types (26.5%), and 118 cases were unknown (24.1%). Among the study population, 272 patients (55.5%) had PE, and 218 (44.5%) had no PE. Pathological examinations were performed in 73 patients diagnosed with PE, in which 45 patients (61.6%) were diagnosed with MPE. In addition, the general data of patients with PE are shown in Table 1.

Table 1
General data of patients with pleural effusion

Clinical evaluation		Laboratory assessments			
		Blood biochemical index		Urine and bone marrow parameters	
Age	61.49 ± 11.10	White blood cells (× 10 ⁹ /L)	5.7 (4.0-7.7)	Quantitative urine protein (g/24 h)	2.14 (0.65-4.22)
Sex: Male/Female	162/110	Hemoglobin (g/L)	88 (74-107)	β2 microglobulin (μg/ml)	1.46 (0.29-4.06)
D-S stage (Ⅱ/Ⅲ/Ⅳ/unknown)	24/35/209/4	Platelets (× 10 ⁹ /L)	147 (80-243)	Bone marrow plasma cells (%)	26.25 (11-47.625)
Type (Ig A/Ig D/Ig E/Ig G/Light chain/Not secreted/unknown)	53/4/0/70/79/5/61	Erythrocyte sedimentation rate (mm/L)	70 (30-117)		
Extramedullary invasion (no/yes)	54/218	CRP (mg/L)	7.17 (2.46-16.4)		
Osteolytic destruction (no/yes)	121/151	Total protein (g/L)	63.6 (54.25-80.9)		
		Albumin (g/L)	31.85 ± 6.10		
		Calcium (mmol/L)	2.19 ± 0.29		
		LDH (IU/L)	172 (137-215)		
		Creatinine (μmol/L)	104 (72-347.25)		
		Complement C3 (g/L)	0.84 ± 0.26		
		Complement C4 (g/L)	0.258 (0.18-0.32)		
		β2-MG (μg/mL)	4.6 (3.28-9.6)		

Analysis of the differences in laboratory test indexes between patients with and without pleural effusion

Some blood indexes were compared between patients with and without PE before treatment was initiated, and the total protein, albumin, calcium and complement C3 levels were lower in the PE group than in the non-PE group, while the level of β 2-MG was higher in the PE group than in the non-PE group ($P < 0.05$). There were no significant differences in the levels of WBC counts, hemoglobin, platelet counts, red blood cell sedimentation rates, CRP, LDH, creatinine, and complement C4 between the two groups ($P > 0.05$). (Table 2)

Table 2

Comparison of blood test indexes between patients without pleural effusion and patients with pleural effusion

Diagnostic Cytopathology 2018[20]	Case Report	3	3	3	Case 1: N/A
					Case 2: Analysis showed a glucose level of 5.17 mmol/L, a protein level of 30.3 g/L, an LDH level of 3490 IU/L, and an ADA level of 78.6 U/L. The cytological examination revealed many abnormal plasma cells, which constituted approximately 80% of the total nucleated cells in the pleural aspirate.
					Case 3: Routine laboratory blood tests showed a white blood cell count of $6.783 \times 10^9/L$, a hemoglobin level of 74 mg/L, a platelet count of $60 \times 10^9/L$, a total protein level of 96.0 g/L, an albumin level of 24.0 g/L, a globulin level of 72.0 g/L, and a calcium level of 1.86 mmol/L.
Korean J Lab Med 2011[14]	A Case Series in a Single Institution and Literature Review	734	N/A	19	MPE is strongly associated with a predominance of the IgA and IgD subtypes and with aggressive clinical and laboratory characteristics. In particular, the preponderance of IgD myeloma in the MPE patients was an unexpected finding. The incidence of MPE was exceptionally high in IgD myeloma patients compared to the other subtypes. Elevated ADA activity in the pleural fluid can be useful for screening MPE. The high incidence of chromosome 13 abnormality in MPE patients is also significant, since the detection of these abnormalities is a critical prognostic factor for myeloma.
Leukemia & Lymphoma 2009[21]	Clinical Analysis		11	11	The diagnosis of malignant pleural effusion in patients with relapsing/refractory myeloma heralds a poor prognosis despite aggressive local and systemic treatment. Although pleural effusion of a nonneoplastic origin is more common in multiple myeloma, all effusions should be sent for cytological examination. When feasible, flow cytometry for clg/DNA or light chain immunophenotyping is strongly recommended.

Diagnostic Cytopathology 2018[20]	Case Report	3	3	3	Case 1: N/A
Mediterr J Hematol Infect Dis 2012[22]	Case Report	1	1	0	The white blood count was 8700 cells/mm ³ , the hemoglobin level was 10 g/dL, the serum creatinine level was 1.1 mg/dL, and the serum calcium level was 8.8 mg/dL. The serum protein level was 3.7 g/dL, and the albumin level was 2.7 g/dL. Liver function tests were normal. Urinalysis showed 30 mg/dL protein in a spot sample. The level of C-reactive protein was elevated at 50 mg/L. The pleural fluid was exudative with a white blood cell count of 212 cells/mm ³ , with 88% lymphocytes. Fluid triglycerides were elevated at 277 mg/dl, the lactate dehydrogenase level was 133 IU/L and the fluid protein level was 2800 mg/dL. Serum protein electrophoresis showed a total protein level of 3.3 g/dL and an albumin level of 1.6 g/dL; M protein was absent.
SQU Med J 2011[23]	Case Report	1	1	1	A complete blood count (CBC) revealed a white blood cell (WBC) count of $2.2 \times 10^9/L$, an absolute neutrophil count of $0.5 \times 10^9/L$, a Hb level of 8.7 g/dL and a platelet count of $36 \times 10^9/L$. Blood chemistry tests showed an albumin level of 26 g/L, a total protein level of 89 g/L, a glucose level of 5.7 mmol/L, a lactate dehydrogenase (LDH) level of 301 U/L, a β 2 microglobulin level of 12.4 mg/L and a C-reactive protein level of 121 mg/L. Serum calcium, creatinine, uric acid, thyroid stimulating hormone (TSH) and liver enzyme levels were normal. Analysis of the pleural fluid showed a glucose level of 6.0 mmol/L, a protein level of 50 g/L and an LDH level of 172 U/L.

Urine and bone marrow parameters were compared between the two groups before the initiation of treatment, and it turned out that there was no significant differences between the two groups in the levels of urine protein, β 2 microglobulin, and bone marrow plasma cell content ($P > 0.05$). (Table 3)

Table 3
Comparison of urine and bone marrow parameters in patients without pleural effusion

Group	No pleural effusion (218 patients)	Pleural effusion (272 patients)	P-value
White blood cells ($\times 10^9/L$)	5.71 (4.1–7.5)	5.7 (4.0-7.7)	0.908
Hemoglobin (g/L)	91 (79.75–111)	88 (74–107)	0.102
Platelets ($\times 10^9/L$)	165.5 (106.5–224)	147 (80–243)	0.125
Erythrocyte sedimentation rate (mm/L)	78 (32–140)	70 (30–117)	0.058
CRP(mg/L)	4.96 (2.7–14.3)	7.17 (2.46–16.4)	0.450
Total protein (g/L)	72 (63.58–89.5)	63.6 (54.25–80.9)	< 0.001
Albumin (g/L)	33.92 \pm 6.66	31.85 \pm 6.10	< 0.001
Calcium (mmol/L)	2.31 \pm 0.44	2.19 \pm 0.29	< 0.001
LDH(IU/L)	155 (117.5–209)	172 (137–215)	0.085
Creatinine ($\mu\text{mol/L}$)	108.1 (80-263.5)	104 (72-347.25)	0.436
Complement C3 (g/L)	0.92 \pm 0.27	0.84 \pm 0.26	0.007
Complement C4 (g/L)	0.23 (0.165–0.298)	0.258 (0.18–0.32)	0.084
β 2-MG ($\mu\text{g/ml}$)	4.59 (3.19–5.92)	4.6 (3.28–9.6)	0.223
and patients with pleural effusion			

Multiple regression analysis of related indexes in MM patients with pleural effusion

Multiple regression analysis was performed on the above statistically significant parameters, and the results suggest that low total protein and albumin levels are independent risk factors for PE.

Comparison of pleural effusion test results between non-MPE patients and MPE patients

The conventional and biochemical indicators of PE were compared between non-MPE patients and MPE patients, and the results showed that the levels of nucleated cells, total protein, LDH, and ADA (Adenosine deaminase) in the MPE group were higher than those in the non-MPE group ($P < 0.05$). There were no significant differences in specific gravity or the levels of albumin, glucose or CEA (Carcinoembryonic antigen) ($P > 0.05$) between non-MPE patients and MPE patients. (Table 4)

Table 4
Comparison of pleural effusion test results between non-MPE patients and MPE

Group	No pleural effusion (218 patients)	Pleural effusion (272 patients)	P-value
Quantitative urine protein (g/24 h)	2.69(0.45–4.20)	2.14(0.65–4.22)	0.924
β2 microglobulin (μg/ml)	0.83(0.24–4.12)	1.46(0.29–4.06)	0.466
Bone marrow plasma cells (%)	30(14.125–54.475)	26.25(11-47.625)	0.107
Group	Non-MPE patient group (28 patients)	MPE patient group (45 patients)	P-value
Specific gravity (M(Q))	1.021 (1.014–1.026)	1.023 (1.018–1.042)	0.059
Nucleated cells (/mm ³ , M(Q))	160 (68–450)	1680 (136–3200)	0.002
Total protein (g/L, M(Q))	26 (14–36)	38.4 (21.75-60.425)	0.017
Albumin (g/L, M(Q))	16.8 (10.2-18.45)	15.5 (13.15-20.175)	0.542
Glucose (mmol/L, M(Q))	6.54 (5.65–7.5)	6.195 (5.4-8.238)	0.929
CEA (ng/ml, M(Q))	1.11 (0.76–1.68)	0.78 (0.3–1.01)	0.240
LDH (IU/L,M(Q))	76 (54–152)	353 (221-512.5)	< 0.001
ADA (IU/L, M(Q))	6.9 (5.2–8.9)	23.8 (17.9-39.95)	< 0.001
Patients			

Multiple regression analysis of related indexes in MM patients with malignant pleural effusion
Multiple regression analysis was performed on the above statistically significant parameters, and the results suggest that high levels of nucleated cell counts, total protein and ADA, as well as low LDH level in PE were independent risk factors for MPE (Fig. 3).

Table 5 The collection of Case reports on MPE

Diagnostic Cytopathology 2018[20]	Case Report	3	3	3	Case 1: N/A
					Case 2: Analysis showed a glucose level of 5.17 mmol/L, a protein level of 30.3 g/L, an LDH level of 3490 IU/L, and an ADA level of 78.6 U/L. The cytological examination revealed many abnormal plasma cells, which constituted approximately 80% of the total nucleated cells in the pleural aspirate.
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Leukemia & Lymphoma 2009[21]	Clinical Analysis		11	11	The diagnosis of malignant pleural effusion in patients with relapsing/refractory myeloma heralds a poor prognosis despite aggressive local and systemic treatment. Although pleural effusion of a nonneoplastic origin is more common in multiple myeloma, all effusions should be sent for cytological examination. When feasible, flow cytometry for clg/DNA or light chain immunophenotyping is strongly recommended.
Mediterr J Hematol Infect Dis 2012[22]	Case Report	1	1	0	The white blood count was 8700 cells/mm ³ , the hemoglobin level was 10 g/dL, the serum creatinine level was 1.1 mg/dL, and the serum calcium level was 8.8 mg/dL. The serum protein level was 3.7 g/dL, and the albumin level was 2.7 g/dL. Liver function tests were normal. Urinalysis showed 30 mg/dL protein in a spot sample. The level of C-reactive protein was elevated at 50 mg/L. The pleural fluid was exudative with a white blood cell count of 212 cells/mm ³ , with 88% lymphocytes. Fluid triglycerides were elevated at 277 mg/dl, the lactate dehydrogenase level was 133 IU/L and the fluid protein level was 2800 mg/dL. Serum protein electrophoresis

					showed a total protein level of 3.3 g/dL and an albumin level of 1.6 g/dL; M protein was absent.
SQU Med J 2011[23]	Case Report	1	1	1	A complete blood count (CBC) revealed a white blood cell (WBC) count of $2.2 \times 10^9/L$, an absolute neutrophil count of $0.5 \times 10^9/L$, a Hb level of 8.7 g/dL and a platelet count of $36 \times 10^9/L$. Blood chemistry tests showed an albumin level of 26 g/L, a total protein level of 89 g/L, a glucose level of 5.7 mmol/L, a lactate dehydrogenase (LDH) level of 301 U/L, a $\beta 2$ microglobulin level of 12.4 mg/L and a C-reactive protein level of 121 mg/L. Serum calcium, creatinine, uric acid, thyroid stimulating hormone (TSH) and liver enzyme levels were normal. Analysis of the pleural fluid showed a glucose level of 6.0 mmol/L, a protein level of 50 g/L and an LDH level of 172 U/L.

Discussion

The incidence of extramedullary (EM) infiltration in MM is approximately 13% [6], including primary EM disease that is present at the time of initial diagnosis and secondary EM disease that occurs after the progression of MM. A previous study found that the pleura, liver, lungs, breasts, pancreas, lymph nodes, soft tissue, skin, central nervous system, and urogenital system could be involved in EM infiltration. Although the organs or tissues involved in primary and secondary EM disease are different, the results are significant reductions in overall survival (OS) and progression-free survival (PFS). MPE is a very rare complication that occurs when myeloma cells infiltrate the pleura.

In this study, there were 272 (55.5%) and 45 (9.2%) MM patients with PE and MPE, respectively, which were significantly higher than the 6% and 1% reported by previous studies [7, 8]; however, previous results were from single-center studies. Considering that there may be selection bias in different centers, the exact incidence of MM combined with PE or MPE needs to be validated in larger multicenter clinical studies.

In addition, proteasome inhibitors such as carfilzomib and bortezomib are widely used in patients with repetitive/refractory MM, which can lead to adverse reactions, including lung injury, pulmonary hypertension, and respiratory failure. Although adverse events rarely occur, it is still worth noting that the use of such drugs may cause lung injury, which may exacerbate the occurrence of MPE [9-11]. Therefore, the timely and accurate diagnosis of MPE is essential for the adjustment and selection of treatment options. For patients with MM suspected of having MPE, imaging can be used as a preliminary screening method, but PE also needs to be collected for biochemical, cell morphology, and immunological phenotype examinations and immunohistochemical staining of pleural biopsy to support the differential diagnosis.

In our study, patients with PE had lower levels of total protein and albumin than those without PE. Through multiple regression analysis, we found that decreased serum albumin and total protein levels were both risk factors for PE. The main reason might be that the consumption of nutrients by the tumor can lead to anemia, decreased BMI, and hypoproteinemia. Hypoproteinemia is associated with a decrease in the plasma osmotic pressure, which can easily cause the leakage of PE [12]. Furthermore, the production of PE is also related to congestive heart failure, renal insufficiency, and pulmonary embolism secondary to MM.

The complement system is an important immunoregulatory factor and can be activated through the classic, alternative, or lectin pathway. Some previous studies have found that hypocomplementemia is related to MM, and it has been speculated that the complement system is activated through the classic and alternative pathways in the early stages of MM [13, 14]. In this study, we found that MM patients with PE were associated with low complement C3 levels, but the relationship with C4 levels was not statistically significant ($P > 0.05$); this indicated that the formation of PE in MM patients was caused by the activation of the complement bypass pathway. However, further verification is needed.

The presence of MPE indicates a rapid progression of MM and a poor prognosis. The serum LDH level is one of the indicators reflecting the tumor burden. Some previous studies [15, 16] have found that the level of serum LDH was positively correlated with MPE, and its specificity and sensitivity in distinguishing between benign and malignant PE were high. This study showed that the level of LDH in MPE patients was significantly higher than that in non-MPE patients.

Many studies have shown that the level of ADA in MPE patients was lower than that in non-MPE patients; in contrast, this study showed that the level of ADA in MPE patients was significantly higher than that in non-MPE patients ($P < 0.05$). Moreover, some case reports on MM [14, 15, 17] indicated that the level of ADA in MPE patients may be higher than that in non-MPE patients, which is consistent with the results of our study. Thus, the association of the level of ADA with MPE is still controversial. The cause of increased ADA levels in MPE patients may be related to the expression of ADA in a small number of myeloma cells, as well as the activation of inflammatory and T lymphocyte cells [15]. However, the elevated MPE levels in many studies were not caused by MM but by other diseases, primarily tuberculosis.

When the tumor metastasizes to the pleura, the integrity of the walls of the pleural blood vessels is impaired, resulting in high blood vessel permeability and a consequent increase in the concentration of tissue fluid. Therefore, our study showed that the level of total protein in MPE was significantly higher than that in non-MPE, which in turn promoted the formation of MPE. The results of multiple regression analysis showed that a high nuclear cell count, total protein level, and ADA level and a low LDH level in PE were independent risk factors for MPE.

Unfortunately, there is very little research on the correlation between MM and MPE. Yuping Zhong [16] and Young-Uk Cho et al. [14] performed a correlation analysis on MM patients with PE, but the sample size of MPE patients was very small, even fewer than our 45 patients, and other studies only reported individual

patients. In total, these studies lack detailed information on indicators related to MPE and were unable to analyze the mechanisms underlying the development of MPE in MM patients (Table 5)

The treatment of MM has made significant progress in recent years, and a variety of treatment options, such as proteasome inhibitors, immunomodulators, and hematopoietic stem cell transplantation, have greatly improved the prognosis of MM. The prognosis of patients with extramedullary (EM) disease is still poor. Rosiñol L et al ^[24] found that thalidomide was effective in patients with advanced MM but not in patients with EM disease. Monoclonal antibody and chimeric antigen receptor T cell therapy might improve the prognosis ^[25]; however, large sample size studies with long-term follow-up are still needed to confirm the effectiveness of these therapies.

There are some limitations of this study. First, this study was a retrospective study with potential publication bias; thus, the results need to be confirmed by large-scale clinical studies. Second, the clonal evolution and heterogeneity of plasma cells are closely associated with the progression, recurrence and drug resistance of MM. The occurrence of MPE often indicates the end stage of MM. In the future, in-depth studies on the immune function, cytogenetics and molecular biology of MPE patients will be needed to elucidate the pathogenesis.

Conclusion

PE is one of the complications of MM, and it is likely to be MPE. Low serum total protein and albumin levels are independent risk factors for MM with PE. Hypocomplementemia (activation of the complement bypass pathway) may be related to the formation of PE in patients with MM. High levels of total protein, nucleated cell counts and ADA, as well as low LDH levels in PE suggest an increased risk of MPE.

Abbreviations

MM

multiple myeloma

PE

pleural effusion

MPE

myelomatous pleural effusion

CRP

C-reactive protein

LDH

lactate dehydrogenase

WBC

white blood cell

CEA

carcinoembryonic antigen

ADA
adenosine deaminase
EM
extramedullary
PFS
progression-free survival
OS
overall survival

Declarations

Ethical approval: This study was approved by the Biomedical Ethics Committee of West China Hospital of Sichuan University. The Committee's reference number is 2019-52. Written informed consent was obtained from all participants.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: None declared.

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Authors' Contribution: (I) Conception and design: LQY, ZT, ZH; (II) Administrative support: LQY, ZH; (III) Provision of study materials evaluated the combined literatures and drafted the manuscript: LQY, ZT, ZH, ZZH, DYL; (IV) Collection and assembly of data: ZZH, DYL; (V) Data analysis and interpretation: LQY, ZT, ZZH, DYL; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Figures

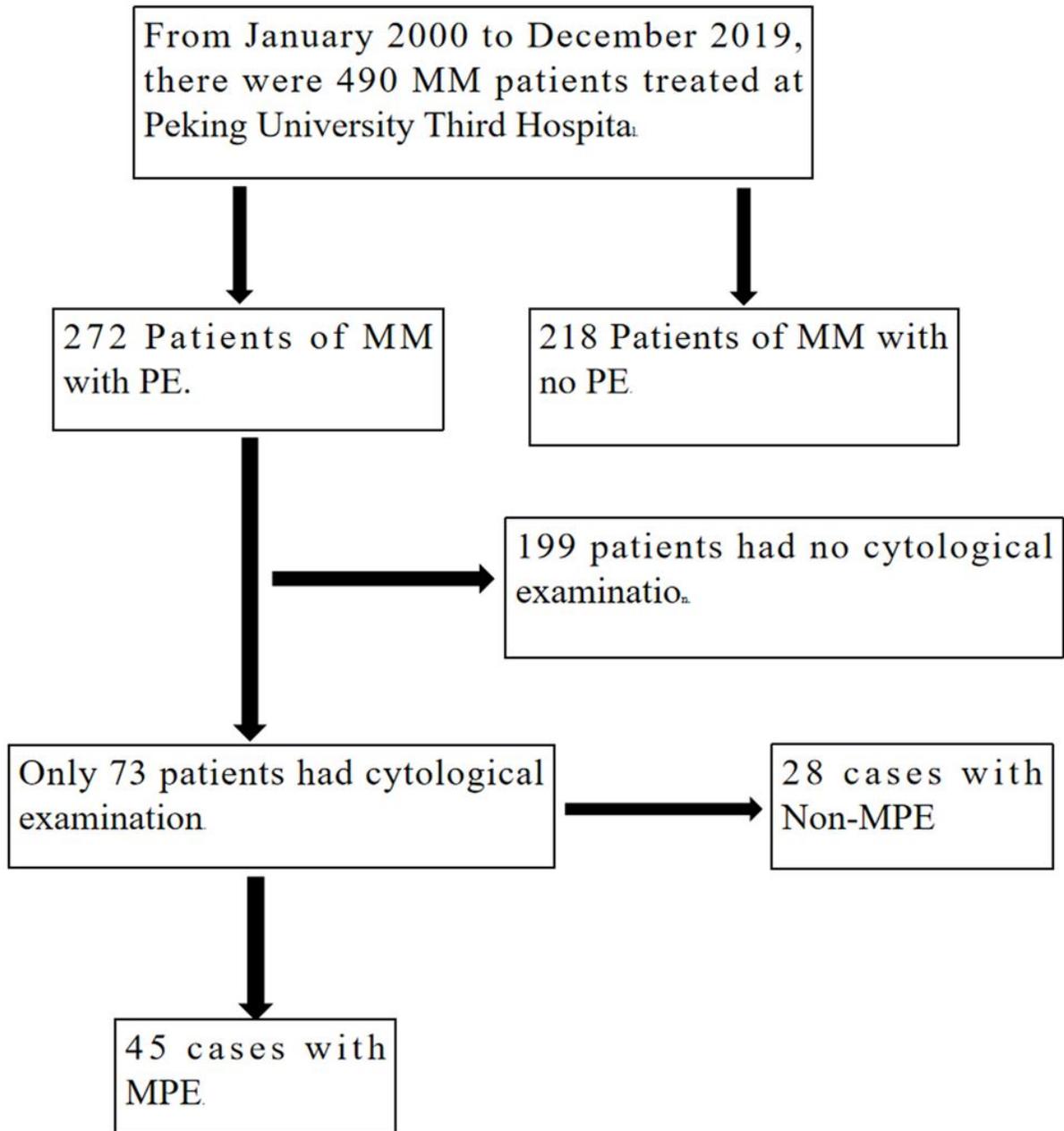


Figure 1

Inclusion criteria and flowchart for MM patients with MPE and the design of the study. MM=Multiple myeloma. PE=Pleural effusion. MPE=Myelomatous pleural effusion.

A

factor	variable name	Coding instructions
Total protein (g / L)	X1	<68=1,68-82=2,>82=3
Albumin (g / L)	X2	<40=1,40-55=2,>55=3
Calcium (mmol / L)	X3	<2.25=1,2.25-2.75=2,>2.75=3
Complement C3 (g / L)	X4	<0.80=1,0.80-1.20=2,>1.20=3
Pleural effusion	Y	None = 0, Yes = 1

B

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Step 1 X1	-.499	.244	4.203	1	.040	.607	.376	.978
X2	-1.270	.592	4.602	1	.032	.281	.088	.896
X3	.230	.277	.691	1	.406	1.259	.732	2.165
X4	-.105	.283	.139	1	.709	.900	.517	1.566
Step 2 X1	-.514	.241	4.564	1	.033	.598	.373	.958
X2	-1.250	.590	4.487	1	.034	.286	.090	.911
X3	.248	.273	.825	1	.364	1.282	.750	2.190
Step 3 X1	-.468	.231	4.093	1	.043	.627	.398	.986
X2	-1.173	.578	4.128	1	.042	.309	.100	.959

Figure 2

Multiple regression analysis of related indexes in MM patients with or without pleural effusion. Fig. 2A shows the variables and assignments in pleural effusion risk factor analysis; Fig. 2B shows the logistic regression.

A

factor	variable name	Coding instructions
Nucleated cells (/mm ³)	X1	0,1,2,3,4 (none = 0, the number will increase step by step)
Total protein (g / L)	X2	0,1,2,3,4 (none = 0, the number will increase step by step)
LDH(IU/L)	X3	0,1,2,3,4,5 (None = 0, the number will increase step by step)
ADA(IU/L)	X4	0,1,2,3,4,5 (None = 0, the number will increase step by step)
Benign and malignant pleural effusion	Y	0 = benign, 1 = malignant

B

Variables in the Equation

		B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
								Lower	Upper
Step 1	X1	26.051	26.422	.972	1	.324	2.061E11	.000	6.378E33
	X2	2.845	4.304	.437	1	.509	17.208	.004	79378.467
	X3	-6.187	6.987	.784	1	.376	.002	.000	1821.497
	X4	16.028	16.139	.986	1	.321	9137870.590	.000	4.992E20

Figure 3

Multiple regression analysis of related indexes in MM patients with malignant pleural effusion. Fig.3A shows the variables and assignments in malignant pleural effusion risk factor analysis; B shows the logistic regression.