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The presence of pleural effusion is an independent prognostic factor in patients with malignant pleural mesothelioma

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Malignant pleural mesothelioma (MPM) is a rare form of thoracic malignancy with a poor prognosis. Pleural effusion (PE) occurs in the majority of patients with MPM; however, its impact on MPM outcomes remains controversial. We searched for eligible patients from the Surveillance, Epidemiology, and End Results (SEER) database, and clinicopathological information and outcomes were collected. Cox proportional hazard regression analyses were utilized to evaluate the association of PE and other factors with overall survival (OS) and cancer-specific survival (CSS) in patients with MPM. A total of 4185 patients were extracted from the SEER database from 2000 to 2021. The median age of the cohort was 73 years, with a predominance of male patients and epithelioid MPM as the main histological subtype. Univariate Cox regression revealed associations between PE, age, sex, marital status, histology, stage, and treatment with both OS and CSS. Besides, multivariate analyses indicated that PE was independently associated with poorer OS and CSS in patients with MPM, regardless of age, sex, histology, stage, and treatment. Subgroup analyses suggested that PE has a remarkable impact on patients undergoing surgery. PE might serve as an independent prognostic factor in patients with MPM, especially in surgery recipients. Consequently, the development of pleural effusion in these patients should receive increased attention. Future studies are needed to validate these findings, particularly concerning the effect of PE in other clinical settings, such as immunotherapy.

Keywords Malignant pleural mesothelioma, Pleural effusion, Prognosis, SEER

Malignant mesothelioma is a rare malignancy originating from mesothelial cells, with malignant pleural mesothelioma (MPM) being the main form. It is confirmed that some occupational exposures, such as asbestos and erionite, play critical roles in the development of MPM[1,2]. Additionally, iatrogenic exposure to radiotherapy could also increase the risk of developing second malignancies, including malignant mesothelioma[3]. The latest epidemiological data from World Health Organization (WHO) revealed that approximately 30,000 new cases and new deaths of mesothelioma occurred globally each year, accounting for 0.2% and 0.3% of all malignancies, respectively[4]. Although not common in clinical settings, the disease burden of MPM should not be underestimated due to the lack of curative treatment and poor prognosis, of which the median survival is less than 2 years, with a low 5-year survival rate[5,6]. MPM is mainly classified into three histological subtypes: epithelial, biphasic, and sarcomatoid[7]. Among them, the epithelioid subtype is associated with better prognosis, whereas patients with sarcomatoid histology had the worst outcomes, with a median survival of only 4 months[8,9]. Meanwhile, MPM is often accompanied by pleural effusion (PE) on initial diagnosis or during disease development, and it is proved that the presence of PE can lead to worse life quality[10]. However, limited evidence focused on the prognostic role of PE on MPM. This study aimed to explore the prognostic impact of PE in patients with MPM.

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Methods

Ethics declarations and study design

This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee on Biomedical Research of West China Hospital with informed consent waived due to the retrospective design (2024 – 616). Patients were retrospectively retrieved from Surveillance, Epidemiology, and End Results (SEER) Research Data, 17 Registries (2000–2021), using the SEER*Stat 8.4.3. The diagnosis of MPM was based on a combination of two fields: Primary Site - labeled (C34.0-C34.8, C38.4) and ICD-O-3 Hist/behav (9050/3-9055/3) according to previous studies[11]. Besides, the definition of PE was according to the variable of Pleural Effusion Recode (2010+), which was based on imaging and pleural fluid evidence when enrolling in the database. Patients meeting the following criteria were included: (1) diagnosed with MPM; (2) ≥ 18 years old. The exclusion criteria were as follows: (1) not microscopically confirmed; (2) lack of information on PE; (3) multiple primary tumors; (4) lack of prognostic data; (5) survival of less than one month; (6) unclear tumor stage.

Patient selection

As Fig. 1 showed, we initially identified 14,488 cases with MPM, and 10,303 cases were removed according to exclusion criteria. Ultimately, 3,661 patients with concomitant PE and 524 patients without PE were included.

Data collection and outcome definitions

Variables collected included age, sex, marital status, race, diagnostic year, tumor histology, stage, treatment (surgery, radiotherapy, and chemotherapy), and outcomes (overall survival (OS) and cancer-specific survival (CSS)). Notably, the fibrous histology in the SEER database consists of multiple forms of sarcomatoid mesotheliomas[12], and results were presented in the original term rather than 'sarcomatoid', which is more commonly used.

OS was the duration from MPM diagnosis to last follow-up or death, while CSS was defined as the time between initial diagnosis and death caused by MPM or last follow-up.

Statistical analyses

Measurement data were presented as medians with interquartile ranges (IQRs), and discrepancies between patients with and without PE were assessed by Wilcoxon rank sum test. Categorical data were presented as frequencies with percentages, with Chi-squared test and Fisher's exact test evaluating the differences between the two groups. Kaplan-Meire curves and log-rank tests were applied to assess the survival differences between PE and non-PE groups. Moreover, associations of clinicopathological factors with outcomes were investigated by Cox proportional hazards regression. Subgroup analyses were conducted to detect the robustness and identify

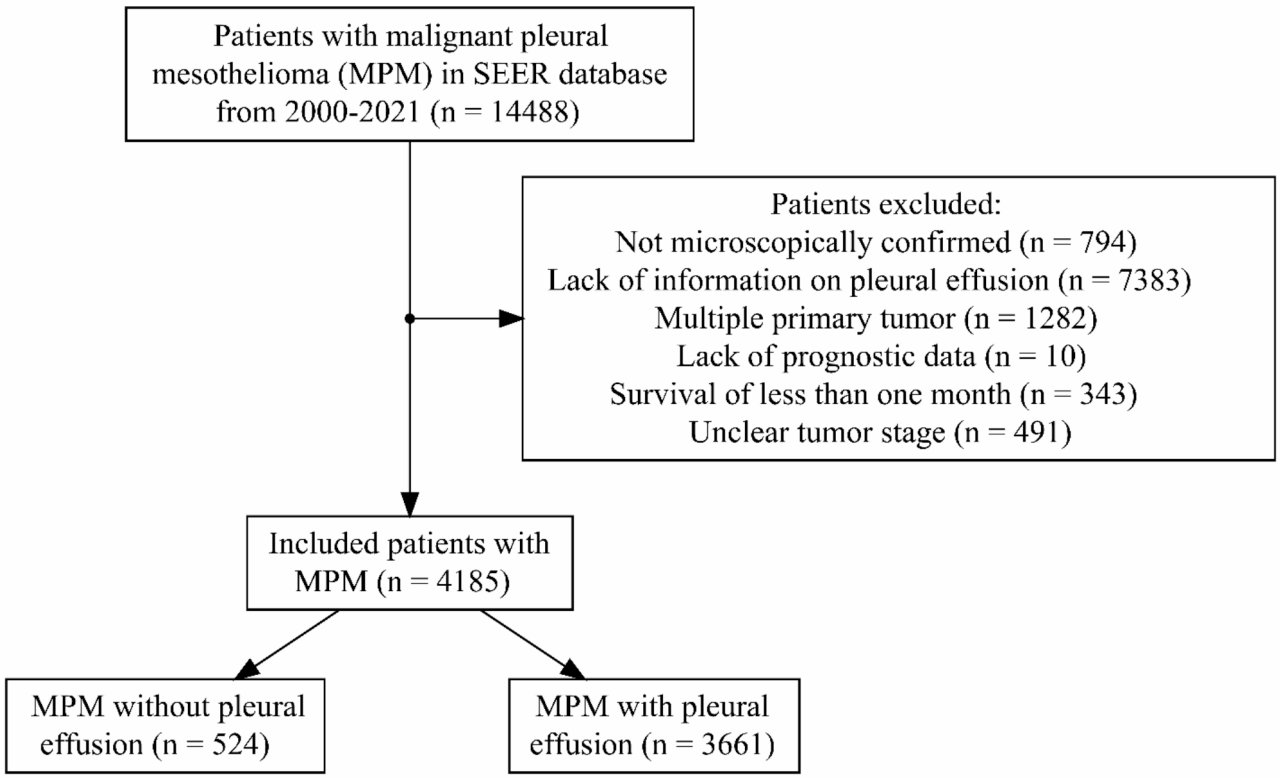

Fig. 1. Flowchart of the patient selection.

the benefiting population. Statistical significance was defined as a two-tailed p-value of less than 0.05. R 4.2.2 was employed for statistical analyses.

Results

Patient characteristics

4,185 patients with MPM were included, and the median OS and CSS were 10 and 11 months, respectively. The median age was 73 years, and most cases were male, white race, married, and had coexistent PE, while approximately half of the cases were stage IV with epithelioid histology (Table 1). More than half of patients received chemotherapy, while only a minority underwent surgery or radiotherapy. No significant differences were observed in most factors. However, it appeared that the PE group had more males and epithelioid histology but fewer radiotherapy recipients (Table 1).

Association of pleural effusion with survival in MPM

As Fig. 2 showed, patients with PE had significantly poorer OS and CSS compared to those without PE. Besides, the 5-year OS rates were 5.87% and 10.80% in patients with and without PE, while the 5-year CSS rates were 7.33% and 14.20% in the two groups, respectively.

The results of univariate Cox proportional hazards regression indicated that the presence of PE was negatively associated with both OS and CSS (OS: HR = 1.13, 95%CI: 1.02–1.25; $p = 0.019$; CSS: HR = 1.17, 95%CI: 1.05–

Characteristic	Overall $N = 4,185$	Without PE $N = 524$	With PE $N = 3,661$	*P*-value
Age, Median (IQR)	73 (66–80)	73 (66–79)	73 (66–80)	0.057
Age, n (%)				0.200
<65	854 (20)	118 (23)	736 (20)	
≥65	3,331 (80)	406 (77)	2,925 (80)	
Sex, n (%)				0.033
Female	1,010 (24)	146 (28)	864 (24)	
Male	3,175 (76)	378 (72)	2,797 (76)	
Marital status, n (%)				0.140
Married	2,870 (69)	374 (71)	2,496 (68)	
Others	1,315 (31)	150 (29)	1,165 (32)	
Race, n (%)				0.680
White	3,748 (90)	465 (89)	3,283 (90)	
Asian	176 (4.2)	23 (4.4)	153 (4.2)	
Black	219 (5.3)	33 (6.3)	186 (5.1)	
Indian or Alaska	26 (0.6)	3 (0.6)	23 (0.6)	
Unknown	16	0	16	
Stage, n (%)				0.042
I	946 (23)	102 (19)	844 (23)	
II	423 (10)	50 (9.5)	373 (10)	
III	998 (24)	149 (28)	849 (23)	
IV	1,818 (43)	223 (43)	1,595 (44)	
Histology, n (%)				<0.001
Epithelioid	1,855 (44)	184 (35)	1,671 (46)	
NOS	1,398 (33)	183 (35)	1,215 (33)	
Fibrous	505 (12)	104 (20)	401 (11)	
Biphasic	427 (10)	53 (10)	374 (10)	
Surgery, n (%)				0.570
No or unknown	3,039 (73)	386 (74)	2,653 (72)	
Yes	1,146 (27)	138 (26)	1,008 (28)	
Radiotherapy, n (%)				<0.001
No or unknown	3,659 (87)	395 (75)	3,264 (89)	
Yes	526 (13)	129 (25)	397 (11)	
Chemotherapy, n (%)				0.920
No or unknown	1,829 (44)	228 (44)	1,601 (44)	
Yes	2,356 (56)	296 (56)	2,060 (56)	

Table 1. Baseline characteristics of included patients. Abbreviations: PE: pleural effusion; IQR: interquartile range; NOS: not otherwise specified.

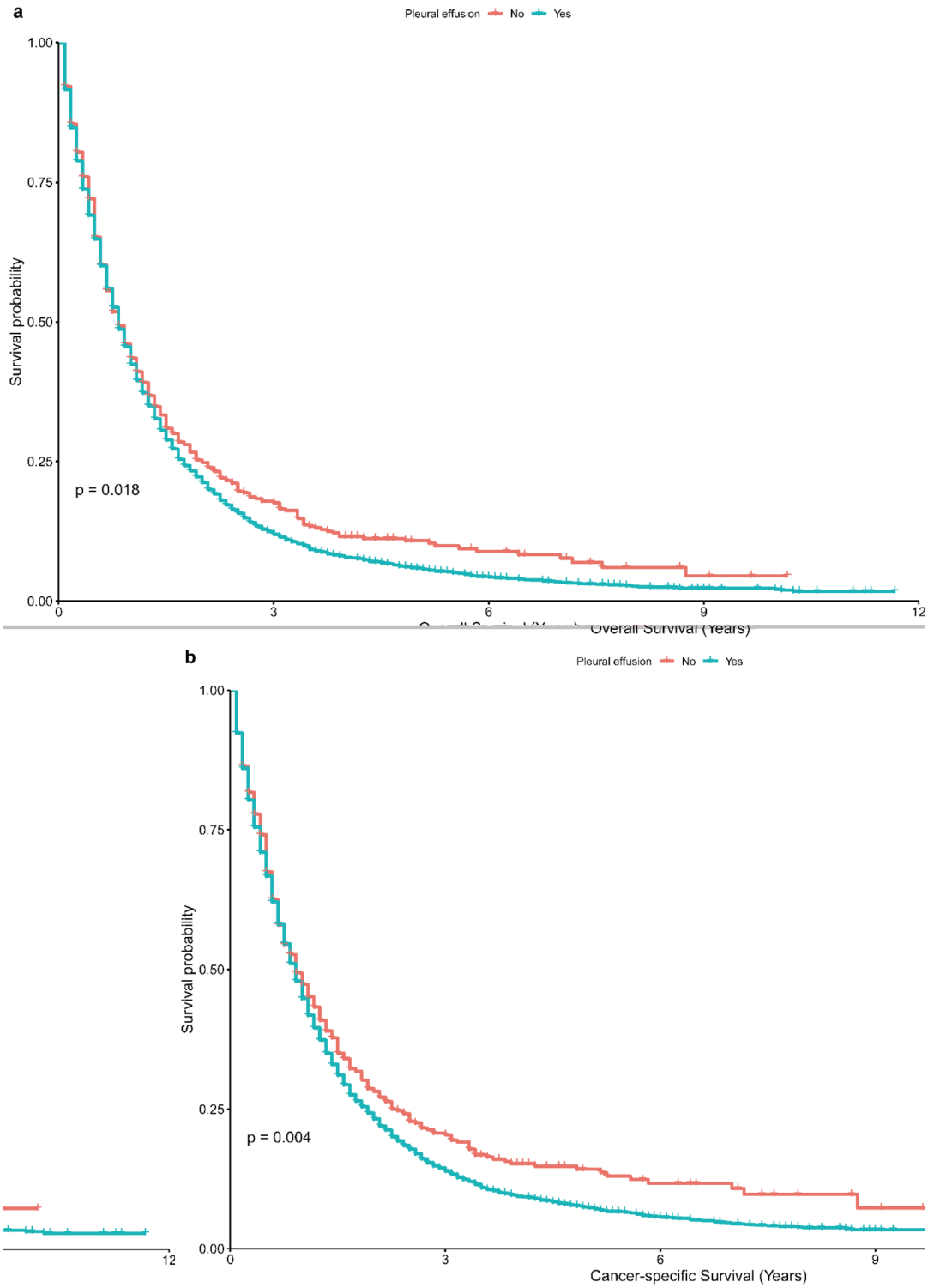

Fig. 2. Kaplan-Meier curves of the association of PE with (**a**) OS and (**b**) CSS.

1.29, $p = 0.004$) (Table 2), and significant results were also observed in age, sex, marital status, histology, stage, and treatment. However, results of race were non-significant.

Further multivariate analyses demonstrated that the presence of PE was independently related to worse OS and CSS, even after adjustment (OS: HR = 1.20, 95%CI: 1.08–1.33, $p < 0.001$; CSS: HR = 1.25, 95%CI: 1.12–1.39, $p < 0.001$) (Table 3). Notwithstanding, the impact of radiotherapy did not remain significant.

	OS		CSS	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age				
<65	1.00 (reference)		1.00 (reference)	
≥65	1.55 (1.42–1.68)	**<0.001**	1.52 (1.40–1.66)	**<0.001**
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.25 (1.16–1.35)	**<0.001**	1.25 (1.16–1.36)	**<0.001**
Marital status				
Married	1.00 (reference)		1.00 (reference)	
Others	1.15 (1.07–1.23)	**<0.001**	1.14 (1.06–1.22)	**<0.001**
Race				
White	1.00 (reference)		1.00 (reference)	
Non-white	0.96 (0.86–1.07)	0.466	0.95 (0.85–1.07)	0.409
Histology				
Epithelioid	1.00 (reference)		1.00 (reference)	
NOS	1.52 (1.41–1.64)	**<0.001**	1.51 (1.39–1.63)	**<0.001**
Fibrous	2.44 (2.19–2.71)	**<0.001**	2.46 (2.21–2.74)	**<0.001**
Biphasic	1.52 (1.36–1.70)	**<0.001**	1.54 (1.38–1.73)	**<0.001**
Pleural effusion				
No	1.00 (reference)		1.00 (reference)	
Yes	1.13 (1.02–1.25)	**0.019**	1.17 (1.05–1.29)	**0.004**
Stage				
I-II	1.00 (reference)		1.00 (reference)	
III-IV	1.27 (1.18–1.36)	**<0.001**	1.31 (1.21–1.40)	**<0.001**
Surgery				
No or unknown	1.00 (reference)		1.00 (reference)	
Yes	0.60 (0.56–0.65)	**<0.001**	0.60 (0.56–0.65)	**<0.001**
Radiotherapy				
No or unknown	1.00 (reference)		1.00 (reference)	
Yes	0.82 (0.74–0.90)	**<0.001**	0.82 (0.74–0.91)	**<0.001**
Chemotherapy				
No or unknown	1.00 (reference)		1.00 (reference)	
Yes	0.63 (0.59–0.67)	**<0.001**	0.64 (0.60–0.69)	**<0.001**

Table 2. Univariate Cox proportional hazards regression for OS and CSS in patients with MPM. Abbreviations: OS: overall survival; CSS: cancer-specific survival; HR: hazard ratio; CI: confidence interval; NOS: not otherwise specified. Significance values are in bold.

Subgroup analyses

Subsequently, subgroup analyses were performed to investigate the prognostic impact of PE in different populations. The results were robust in a majority of subgroups (Figs. 3 and 4). Furthermore, a significantly worse impact of PE on both OS and CSS was observed in patients receiving surgery (OS: HR = 1.37, 95%CI: 1.12–1.68, $p = 0.002$, $p_{interaction} = 0.029$; CSS: HR = 1.44, 95%CI: 1.16–1.79, $p = 0.001$, $p_{interaction} = 0.029$), while PE showed non-significant effects in patients not receiving surgical intervention. Interestingly, the results regarding radiotherapy were different to some extent because patients who did not receive radiotherapy appeared to be more affected by PE, but only result of OS had significant interaction (OS: HR = 1.17, 95%CI: 1.04–1.32, $p = 0.007$, $p_{interaction} = 0.022$; CSS: HR = 1.20, 95%CI: 1.06–1.35, $p = 0.003$, $p_{interaction} = 0.070$). Fibrous histology seemed to be more affected by PE than other subtypes but without a significant difference from other histological subgroups (OS: HR = 1.40, 95%CI: 1.11–1.77, $p = 0.004$, $p_{interaction} = 0.258$; CSS: HR = 1.41, 95%CI: 1.11–1.79, $p = 0.004$, $p_{interaction} = 0.470$). However, no significant results were observed in the subgroups of male sex, NOS or biphasic histology, and chemotherapy, with no evidence of interaction.

Discussion

Though the presence of PE in MPM is common, few studies hitherto mentioned its role in MPM. The present study focused on the prognosis of MPM with PE and found that patients with PE have worse OS and CSS than patients without PE by multivariable analysis adjusting previously reported prognostic factors. In addition, subgroup analyses revealed that the presence of PE showed better prognostic effect in patients receiving surgical intervention than those not receiving resection, while the differences of effect between subgroups were still controversial in radiotherapy and chemotherapy recipients.

	OS		CSS	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age				
<65	1.00 (reference)		1.00 (reference)	
≥65	1.33 (1.22–1.45)	**<0.001**	1.32 (1.21–1.44)	**<0.001**
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.21 (1.12–1.31)	**<0.001**	1.20 (1.11–1.31)	**<0.001**
Marital status				
Married	1.00 (reference)		1.00 (reference)	
Others	1.12 (1.04–1.20)	**0.003**	1.11 (1.03–1.19)	**0.009**
Histology				
Epithelioid	1.00 (reference)		1.00 (reference)	
NOS	1.38 (1.28–1.49)	**<0.001**	1.37 (1.27–1.48)	**<0.001**
Fibrous	2.26 (2.03–2.51)	**<0.001**	2.29 (2.05–2.56)	**<0.001**
Biphasic	1.62 (1.45–1.81)	**<0.001**	1.65 (1.47–1.85)	**<0.001**
Pleural effusion				
No	1.00 (reference)		1.00 (reference)	
Yes	1.20 (1.08–1.33)	**<0.001**	1.25 (1.12–1.39)	**<0.001**
Stage				
I-II	1.00 (reference)		1.00 (reference)	
III-IV	1.42 (1.32–1.52)	**<0.001**	1.45 (1.35–1.57)	**<0.001**
Surgery				
No or unknown	1.00 (reference)		1.00 (reference)	
Yes	0.70 (0.64–0.75)	**<0.001**	0.69 (0.63–0.75)	**<0.001**
Radiotherapy				
No or unknown	1.00 (reference)		1.00 (reference)	
Yes	0.94 (0.85–1.04)	0.220	0.94 (0.85–1.05)	0.286
Chemotherapy				
No or unknown	1.00 (reference)		1.00 (reference)	
Yes	0.67 (0.62–0.72)	**<0.001**	0.68 (0.64–0.73)	**<0.001**

Table 3. Multivariate Cox proportional hazards regression for OS and CSS in patients with MPM. Abbreviations: OS: overall survival; CSS: cancer-specific survival; HR: hazard ratio; CI: confidence interval; NOS: not otherwise specified. Significance values are in bold.

PE is a common complication of various malignancies, especially MPM[13]. It is known that many malignant pleural effusion (MPE) cases are caused by pleura metastases of tumors, frequently indicating a poor prognosis[14]. Moreover, PE may also lead to symptoms of chest tightness, cough, and dyspnea, which could further affect the treatment response and even cause treatment withdrawal[15]. Consequently, it is reasonable that the presence of PE has a negative effect on the survival of MPM. However, the role of PE in MPM is still under debate. Asciak and colleagues retrospectively analyzed 761 MPM patients and proposed that MPE may be a bystander, as they found non-significant association between PE exposure duration and survival[16]. However, these findings were based on limited follow-up, which might contribute to the differences from our results. Conversely, other studies supported that PE could shorten the survival of MPM patients, particularly those with non-expandable lungs, which iss consistent with ours[15,17,18]. Interestingly, an experimental study demonstrated the biological potency of MPE to promote the migration and metastasis of mesothelioma cells with the mediation of numerous growth factors or cytokines, indicating the contributing role of PE in disease progression of MPM[19]. These mechanisms may explain our conclusions to some extent.

Current treatment approaches, including surgical resection, chemotherapy, and radiotherapy have shown efficacy in patients with MPM, which was validated in our study. However, improvements in clinical outcomes are still limited, especially for unresectable diseases[20]. Previous research revealed that MPE impairs the cytotoxic effects of pemetrexed/cisplatin[19], while our subgroup analyses showed a strong trend of negative correlation. Furthermore, we first found that patients undergoing surgery for MPM may be remarkably affected by PE, suggesting that clinicians may be more concerned about the presence of PE in MPM patients, especially as a postoperative complication, and perioperative monitoring, may help prolong the prognosis and improve the quality of life. Novel evidence confirmed that immune checkpoint inhibitors (ICIs) have achieved good benefits in MPM[21–23]. However, due to the lack of relevant information in SEER database, the effect of PE on immunotherapy recipients was not analyzed, and it is hoped that future studies could be carried out to resolve the issue.

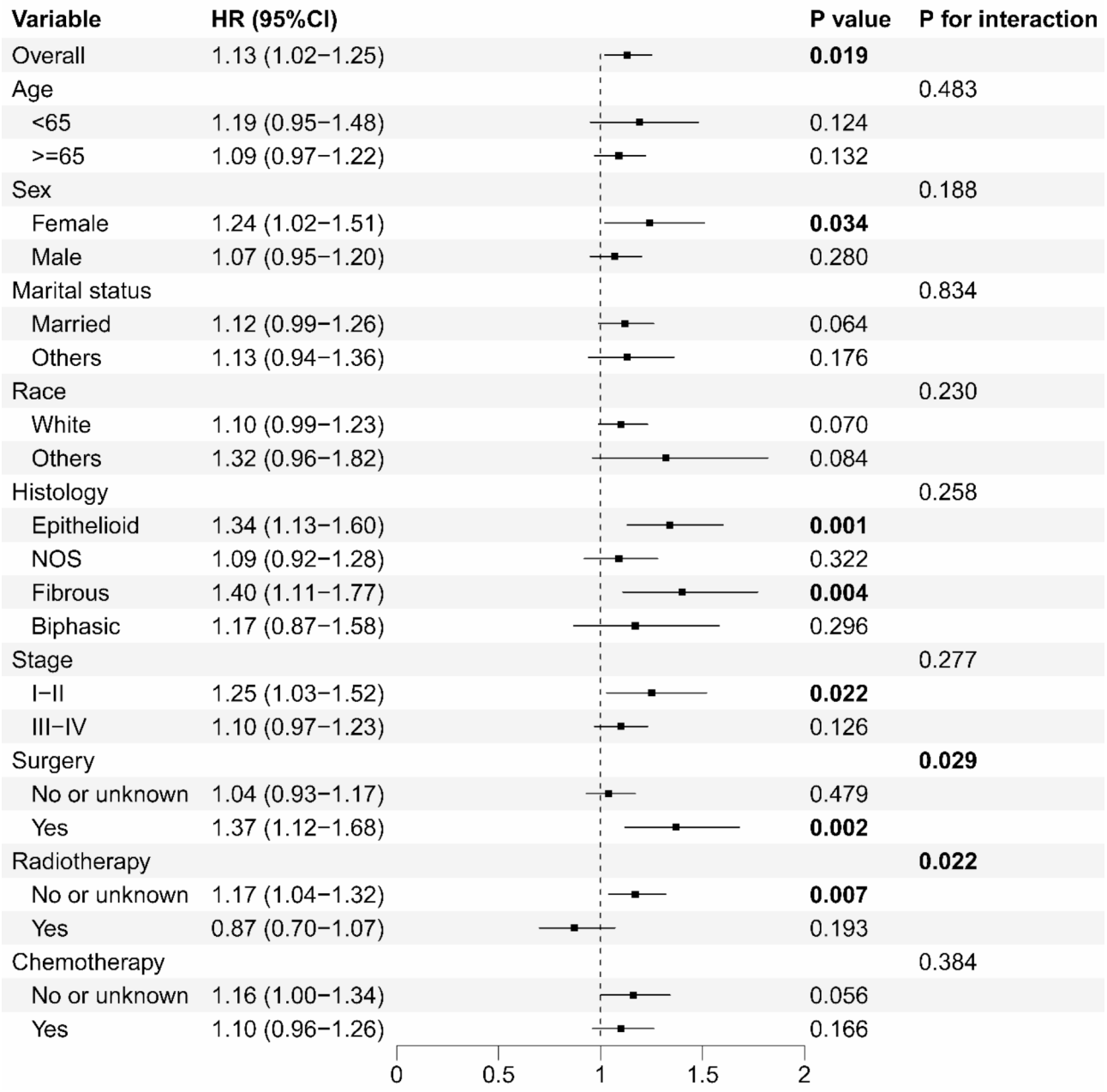

Fig. 3. Forest plot of the subgroup analyses for OS.

There are also some limitations. First, the study was retrospective in design; however, the sample size was large enough and the baseline characteristics were balanced, reflecting a low risk of bias. Second, some covariates were not analyzed due to a lack of data, for instance, the combination of treatments, and the type of combination (adjuvant or neoadjuvant). Nevertheless, multivariate analyses were conducted to maximally adjust the results. Third, some specific characteristics of PE cannot be analyzed. For instance, the effusion-specific treatment like talc, video-assisted thoracoscopic surgery (VATS), and indwelling catheter therapy may also affect the clinical outcomes of patients. Besides, the time point of PE presence is also important since the PE presence before or after treatment may show different effects. However, these covariates could not be collected due to the unavailability in the SEER database. Hence, further prospective studies are needed to explore the effect of these aspects in MPM with PE.

Conclusions

Generally, the presence of PE could serve as an independent prognostic factor in patients with MPM, and patients receiving surgical resection may be remarkably affected. Therefore, the monitoring and management of PE are crucial in the treatment of MPM. However, future prospective studies are needed to explore its impact on systemic therapies, particularly on patients treated with checkpoint inhibitors.

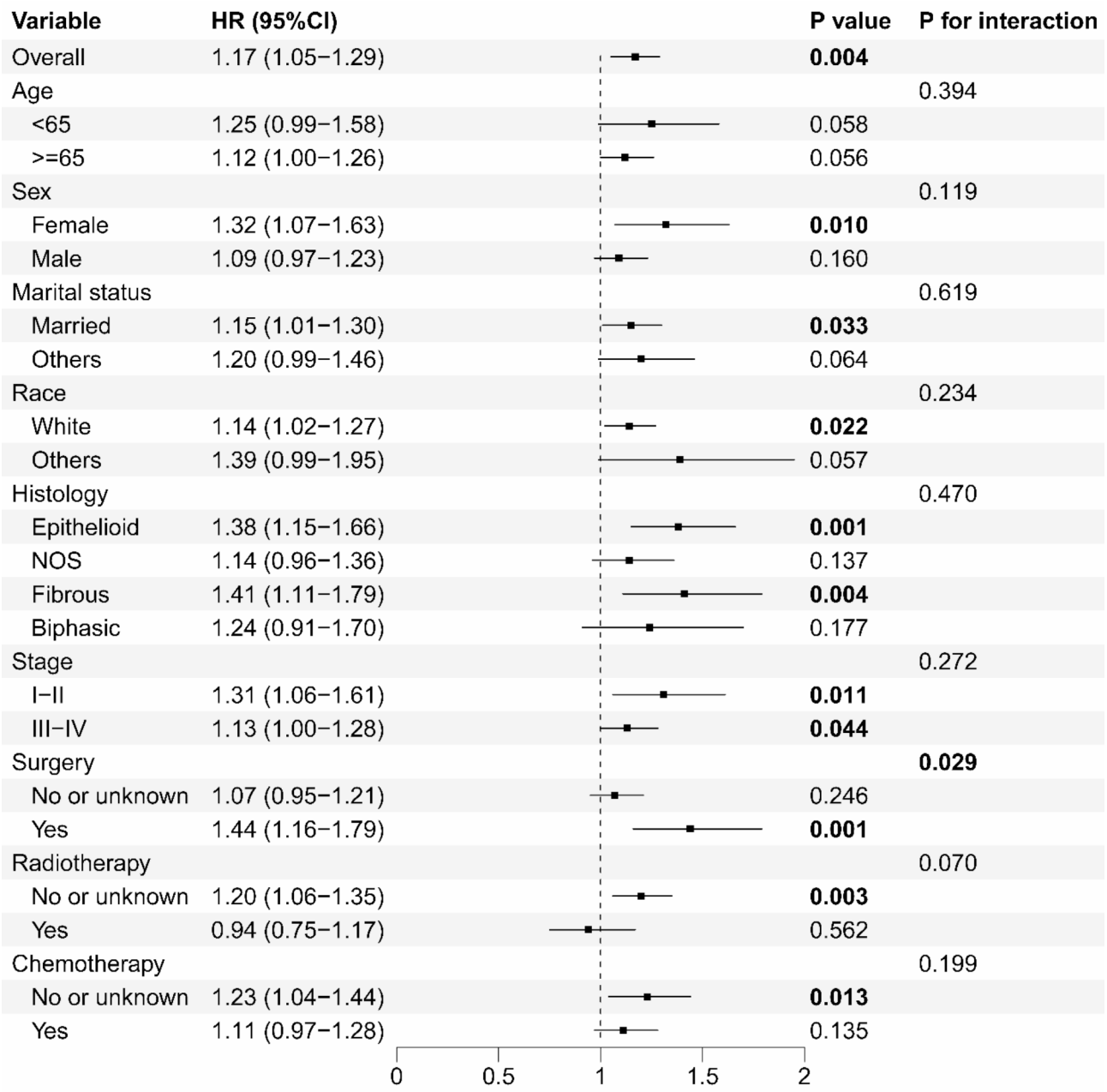

Fig. 4. Forest plot of the subgroup analyses for CSS.

Data availability

Data from this study could be accessed in the SEER database, which is publicly available (https://seer.cancer.gov/).

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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