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*Original Article*

# Characteristics and negative impacts of pleural effusion in hospitalized patients undergoing maintenance hemodialysis

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**Abstract:** Background: Hospitalized patients on maintenance hemodialysis often develop pleural effusion (PE). The prognosis of these patients is likely to be affected by the PE. This study examined the characteristics of PE, identified risk factors for its development, and explored its negative effects. Methods: In this retrospective study, we analyzed medical records of 1,077 patients who underwent maintenance hemodialysis between October 2014 and January 2022. According to the chest computed tomography (CT) imaging results, patients were categorized into two groups: PE and non-PE. A definitive diagnosis of PE was made after a nephrologist, a pulmonary physician, and a radiologist reviewed the case. Results: Of the 1,077 patients, 343 (31.85%) were diagnosed with PE. These patients had a mean age of 55.28±15.21 years old and 61.47% of them were men. There were 77.84% patients with PE resulting from heart failure, and 82.02% of these patients had bilateral effusions. The occurrence of PE was associated with cardiovascular disease, clinic-systolic blood pressure (SBP), chest tightness, leg edema, and pro-brain natriuretic peptide (pro-BNP). PE patients had a poorer survival rate than patients without PE (unadjusted hazard ratio [HR]: 4.17; 95% CI: 3.12-5.57). The survival rates of patients with small PE did not differ from those with moderate to large PE. Similarly, no difference was found in survival between the bilateral PE and unilateral PE groups, as well as between the heart failure and non-heart failure groups. Conclusions: Hospitalized patients undergoing maintenance hemodialysis have a high incidence of PE. PE (even a small amount) is an risk factor for increased mortality. These poor prognostic features should be noted by physicians and managed accordingly.

**Keywords:** Pleural effusion, hemodialysis, incidence, risk factors, survival

## Introduction

End-stage renal disease (ESRD) has a major effect on global health and is a direct cause of global morbidity and mortality; the related cost in terms of financial and human resources is immense [1]. After the 1960s, the availability of renal replacement therapy (RRT), which is life-saving, has made the long-term outlook for patients with ESRD favorable [2]. Despite the fact that a growing number of patients have or need functional kidney transplants, the availability of organs for transplantation has not grown correspondingly [3]. The most common form of treatment today is center hemodialysis. Prevalence of the disease and worldwide use of RRT are expected to rise sharply in the next decade. Studies have reported that the number of people receiving RRT exceeds 2.5 million and is projected to double to 5.4 million by 2030 [4, 5]. Due to the increased use of maintenance hemodialysis and the increasing life expectancy of patients with ESRD, complications are becoming more common. Many extrathoracic and thoracic problems may arise in such patients. The dialysis itself is often associated with an array of thoracic complications; pleural effusion (PE) is one common problem among them [6].

Current correlative research indicates different incidences of PE in patients undergoing maintenance hemodialysis. In 1983, one study reported that 7.7% of hemodialysis patients suffered PE, and the majority of patients with PE were asymptomatic [7]. Another study has focused on thoracic problems in symptomatic hemodialysis patients and showed that the symptoms included cough, dyspnea, low-grade pyrexia, malaise, and weight loss, and as many as 45.3% of uremic patients developed PE [8]. The largest study to date reported a PE incidence of 20.6% of PE in hospitalized patients undergoing maintenance hemodialysis; of the 311 hospital admissions, 247 did not have PE, while PE was present in the remaining 64 [9]. The incidence of PE among Chinese patients with ESRD is unknown. Infection, pulmonary embolism, inflammatory pleuritis, and thoracic surgery are all local factors that contribute to PE development, and systemic factors include heart failure, liver disease, and renal disease, [10]. Two prospective observational studies evaluated the association between PE and mortality. According to a study, patients with malignant effusion had the highest mortality followed by those with congestive heart failure, and bilateral PE is distinctly associated with high mortality [11]. According to another study, bilateral and transudative PE was indicative of higher mortality rates [12]. Until now, only one study has indicated that the existence of PE, regardless of its severity, is significantly associated with lower survival probability in patients undergoing maintenance hemodialysis [13].

Patients with access to dialysis still experience high mortality rates and suboptimal outcomes, as well as high rates of complications and poor health-related quality of life [14]. Despite congestive heart failure representing the leading cause of PE [15], current correlative research is limited, and there is especially a paucity of data on the mortality rates in PE. This implies that we do not have access to clinical information that can enable better evaluation of the prognostic significance of PE. A full understanding of the characteristics and outcome of PE patients may help clinicians appreciate the poor prognostic features and help guide management accordingly. Therefore, in the present study, the medical records of hospitalized patients undergoing maintenance hemodialysis were retrospectively reviewed. Finally, the study enrolled 1,077 patients in order to determine the incidence, clinical characteristics, risk factors, and prognosis of patients with PE.

## Methods

### *Study population*

This was a retrospective study conducted at a single center. A total of 7,779 hospitalized patients undergoing dialysis were identified and were admitted to the Fifth Affiliated Hospital of Sun Yat-sen University (Zhuhai, China) between October 2014 and January 2022. First, we excluded repeat hospitalized patients, and excluded participants according to the following exclusion criteria: maintenance peritoneal dialysis; regular hemodialysis for less than 3 months; only needing temporary dialysis; renal transplantation or death within 3 months; hemodialysis combined with peritoneal dialysis; less than 18 years old. Finally, 1,077 hospitalized patients were enrolled in the current study and were treated with regular hemodialysis (about 3 times per week in 4 hour-sessions). The primary diseases leading to ESRD were as follows: 554 (51.4%) patients had chronic glomerulonephritis; 238 (22.1%) patients had diabetic nephropathy; 120 (11.1%) patients had hypertensive nephropathy; 37 (3.4%) patients had obstructive nephropathy; and 128 (12.0%) patients had other causes.

### *Data collection*

From the electronic medical records and registration records of the blood purification center, detailed medical histories, clinical characteristics, physical examinations, laboratory results, and imaging data were obtained for all patients. In addition, laboratory data included were blood routine, serum albumin, calcium, phosphorus, serum fasting glucose, uric acid, serum creatinine, blood urea nitrogen (BUN), intact parathyroid hormone (iPTH), β2-microglobulin, pro-BNP, high-sensitivity C-reactive protein (hs-CRP), and procalcitonin (PCT). Chest computed tomography (CT) was routinely performed when the patients were admitted to our hospital. Patients were followed up for at least three months post initiation of maintenance hemodialysis or until death. Survival data were

calculated from the date of study entry to the date of death. Surviving patients were censored in January 2022. In the process of collecting data and preparing the manuscript, the confidentiality of patients' data was fully respected.

The study protocol was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (Zhuhai, China), which waived the requirement of obtaining written informed consent from all participants.

*Diagnosis and evaluation*

The chest CT was assessed for the size and location of effusion according to CT imaging features at the midclavicular line, including the anteroposterior quartile and maximum anteroposterior depth. Small anteroposterior effusions were found in the first quartile, moderate effusions in the second quartile, and large effusions in the third and the fourth quartiles [16]. Evaluation of PE was done by a respiratory physician and a radiologist.

The nephrologist and respiratory physician determined the diagnostic category of each PE patient according to the patient's clinical characteristics, laboratory tests, chest CT findings, and clinical course. Patients with congestive heart failure were diagnosed with a history of cardiovascular disease and chest tightness symptoms, signs of excess extravascular lung water and cardiomegaly on chest CT, usually with bilateral effusions, and rapid response to aggressive dialysis. Parapneumonic effusion was diagnosed when the following were present: fever, chest pain, expectoration, an increase in leukocytes and neutrophils, and a unilateral PE associated with a new alveolar infiltrate. A diagnosis of uremic pleurisy was based on chest pain, tightness, unilateral or bilateral PEs, and a slow response to aggressive dialysis. In the current study, other less frequent causes of PE were diagnosed using the usual criteria.

*Statistical analysis*

Data were tested for normal distribution using the Kolmogorov-Smirnov test. A Student's t-test was used to determine whether there were significant differences between the two groups for continuous variables. Non-normally distributed data were described using medians and interquartile ranges, and Mann-Whitney U-tests were used to compare the two sets. Counts and percentages were used for categorical variables, and Fisher's exact probability test or the $x^2$ test was used for comparing groups. PE risk factors were investigated using multivariate logistic regression analyses, and the results were expressed in terms of odds ratio (OR) with 95% confidence interval (CI). The prognostic relevance of PE was assessed using a Cox regression analysis, and the results were expressed in terms of hazard ratio (HR) with 95% CI. Survival was compared using Kaplan-Meier (KM) plots and a log-rank test. Statistical analyses were performed using IBM SPSS Statistics Version 25 (IBM Corp., Armonk, New York, USA). All tests were two-sided, and statistical significance was defined as a *P* value less than 0.05.

## Results

*Demographic and clinical characteristics of study participants*

Data were obtained from a total of 7,779 patients. First, we excluded 5,746 repeat hospitalized patients and then excluded 956 patients according to our predetermined exclusion criteria. Finally, 1,077 patients were included in the analysis (**Figure 1**).

In the 1,077 hospitalized patients, the mean age was 55.28 years old, and 61.47% were men. There were 343 (31.85%) patients diagnosed with PE. Compared with the non-PE group, patients with PE were significantly older and had higher levels of neutrophilic granulocyte percentage (NEUT%), fasting blood glucose (FBG), pro-BNP, hs-CRP, but lower levels of hemoglobin, serum albumin, serum calcium, uric acid, and iPTH. The PE patients were also more prone to diabetes mellitus, hypertension, and cardiovascular disease as well as relatively lower levels of education compared with the non-PE patients. The PE group showed more symptoms of chest tightness, chest pain, expectoration, and leg edema ($P<0.05$) (**Table 1**).

*Incidence and causes of PE*

We found that the incidence of PE at the time of initiating maintenance hemodialysis was

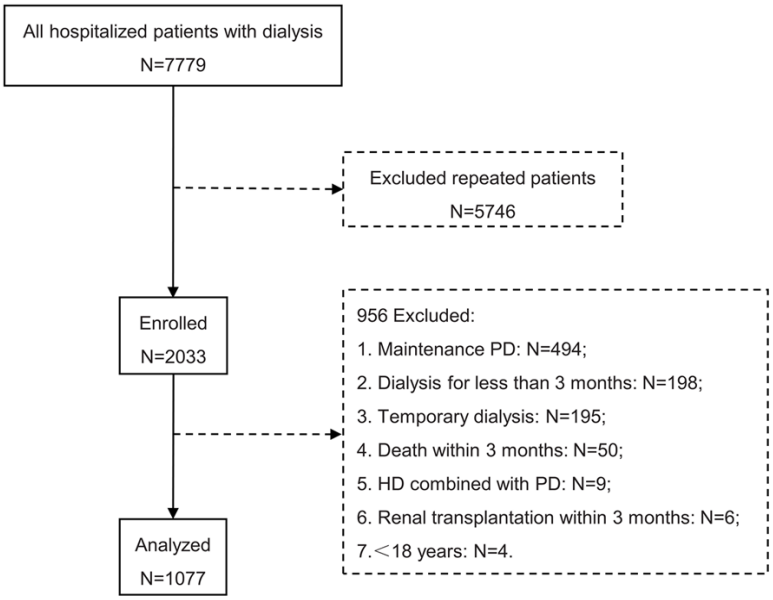


**Figure 1.** Flow chart of the study population. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis.

31.85% (343/1077 patients). Among the 343 patients with PE, there were 262 (76.38%) patients with bilateral PE and 81 (23.62%) patients with unilateral PE; small size PE made up 73.47% of the cases, whereas moderate or large size PE made up 18.66% and 7.87% of the cases, respectively. A total of 27 (7.87%) patients underwent thoracentesis due to intolerable dyspnea. Heart failure was the most common cause of PE (77.84%). Of the non-heart failure causes (20.99%), parapneumonic effusion was the most frequent cause (11.08%), and this was attributed to hypoproteinemia (3.21%), uremic pleurisy (2.62%), malignancy (1.75%), tuberculous pleurisy (1.75%), hepatic hydrothorax (0.58%). In addition, 4 patients had unknown causes (**Table 2**).

*Risk factors for development of PE*

Univariate analysis found that age, body mass index (BMI), diabetes mellitus, hypertension, cardiovascular disease, clinic-systolic blood pressure (SBP), clinic-diastolic blood pressure (DBP), dialysis duration, chest tightness, chest pain, expectoration, leg edema, RBC, NEUT%, LYMP%, FBG, hemoglobin, serum albumin, serum calcium, serum phosphate, serum kalium, serum natrium, serum creatinine, uric acid, iPTH, pro-BNP, hs-CRP, and procalcitonin (PCT) were related to PE (all $P<0.05$) (**Table 1**). Logistic regression analysis was carried out using significant variables obtained from univariate analysis and PE-related variables reported in previous publications, resulting in a final model containing eight variables. Cardiovascular disease, clinic-SBP, chest tightness, leg edema, and pro-BNP were all independent risk factors for the occurrence of PE with the ORs of 1.45 (95% CI: 1.01-2.08), 1.10 (95% CI: 1.03-1.17), 2.17 (95% CI: 1.50-3.16), 2.19 (95% CI: 1.53-3.13), and 1.05 (95% CI: 1.04-1.07), respectively. In contrast, the BMI, hemoglobin, and serum albumin were protective factors that prevented the occurrence of PE, and the ORs were 0.94 (95% CI: 0.90-0.99), 0.98 (95% CI: 0.98-0.99), and 0.88 (95% CI: 0.85-0.90), for these measurements, respectively (**Table 3**).

*Survival analysis*

During follow-up, a total of 192 all-cause deaths (including 118 deaths from the PE group, and 74 deaths from the non-PE group) were recorded. Kaplan-Meier survival plots showed that the presence of PE was significantly associated with lower survival probability ($P<0.0001$). Among PE patients, there was no significant difference in survival rates among PE patients, with small PE and those with moderate to large PE having similar survival ($P = 4087$); survival rates were also not different for bilateral PE patients and unilateral PE patients ($P = 3018$). Similarly, there was no difference in survival between the heart failure and the non-heart failure groups ($P = 8827$) (**Figure 2**).

The presence of PE was significantly associated with a lower probability of survival (HR: 4.17; 95% CI: 3.12-5.57). After adjusting for age, BMI, diabetes mellitus, cancer, cardiovascular disease, clinic-SBP, dialysis duration, urine volume, hemoglobin, serum albumin, and pro-BNP, the presence of PE was significantly as-

**Table 1.** Clinical characteristics of study participants

| Variable | Total | PE Group | Non-PE Group | *P* value* |
|---|---|---|---|---|
| Number | 1077 | 343 | 734 | |
| Age (y) | 55.28±15.21 | 58.43±15.08 | 53.81±15.06 | <0.001 |
| Male [n (%)] | 662 (61.47) | 212 (61.81) | 450 (61.31) | 0.875 |
| BMI (kg/m$^2$) | 22.23±3.59 | 21.63±3.30 | 22.51±3.69 | <0.001 |
| Smoker [n (%)] | 207 (19.22) | 68 (19.83) | 139 (18.94) | 0.730 |
| Alcohol intake [n (%)] | 77 (7.15) | 23 (6.71) | 54 (7.36) | 0.699 |
| Diabetes mellitus [n (%)] | 331 (30.73) | 135 (39.36) | 196 (26.70) | <0.001 |
| Hypertension [n (%)] | 926 (85.98) | 309 (90.09) | 617 (84.06) | 0.008 |
| Cardiovascular disease [n (%)] | 273 (25.35) | 129 (37.61) | 144 (19.62) | <0.001 |
| Cancer [n (%)] | 71 (6.59) | 30 (8.75) | 41 (5.59) | 0.051 |
| Clinic-SBP (mmHg) | 147.20±25.92 | 150.84±25.83 | 145.50±25.80 | 0.002 |
| Clinic-DBP (mmHg) | 84.69±15.94 | 83.11±16.26 | 85.43±15.74 | 0.026 |
| Heart rate (bpm) | 83.88±14.46 | 84.66±16.82 | 83.51±13.20 | 0.265 |
| Dialysis duration (m) | 12.00 (4.00-47.00) | 6.00 (3.00-24.00) | 16.00 (4.00-53.25) | <0.001 |
| Urine volume (ml) | 200.00 (0-700.00) | 250.00 (0-700.00) | 200.00 (0-700.00) | 0.146 |
| *Education background* | | | | 0.001 |
| Illiteracy [n (%)] | 54 (5.01) | 18 (5.25) | 36 (4.90) | |
| Primary school [n (%)] | 259 (24.05) | 105 (30.61) | 154 (20.98) | |
| Middle school [n (%)] | 561 (52.09) | 173 (50.44) | 388 (52.86) | |
| University and above [n (%)] | 203 (18.85) | 47 (13.70) | 156 (21.25) | |
| *Symptoms and signs* | | | | |
| Chest tightness [n (%)] | 241 (22.38) | 134 (39.07) | 107 (14.58) | <0.001 |
| Chest pain [n (%)] | 42 (3.90) | 20 (5.83) | 22 (3.00) | 0.025 |
| Expectoration [n (%)] | 153 (14.21) | 76 (22.16) | 77 (10.49) | <0.001 |
| Fever [n (%)] | 70 (6.50) | 27 (7.87) | 43 (5.86) | 0.212 |
| Leg edema [n (%)] | 244 (22.66) | 129 (37.61) | 115 (15.67) | <0.001 |
| Anorexia [n (%)] | 162 (15.04) | 58 (16.91) | 104 (14.17) | 0.241 |
| Fatigue [n (%)] | 194 (18.01) | 63 (18.37) | 131 (17.85) | 0.836 |
| *Laboratory data* | | | | |
| WBC ($10^9$/L) | 6.40 (4.99-7.99) | 6.36 (4.91-8.26) | 6.41 (5.05-7.85) | 0.737 |
| PLT ($10^9$/L) | 193.10±79.20 | 189.87±81.76 | 194.60±77.98 | 0.370 |
| RBC ($10^{12}$/L) | 3.52±0.88 | 3.25±0.89 | 3.65±0.85 | <0.001 |
| NEUT% (%) | 70.00 (62.90-78.00) | 72.40 (64.40-80.70) | 69.10 (62.40-76.48) | <0.001 |
| LYMP% (%) | 17.20 (11.60-23.40) | 15.60 (10.20-21.60) | 18.25 (12.50-24.50) | <0.001 |
| MONO% (%) | 7.69±3.11 | 7.59±3.27 | 7.74±3.04 | 0.458 |
| Retic% (%) | 1.52 (0.95-2.19) | 1.61 (0.97-2.32) | 1.49 (0.92-2.15) | 0.069 |
| Hemoglobin (g/L) | 98.82±24.05 | 88.36±22.24 | 103.71±23.30 | <0.001 |
| Serum albumin (g/L) | 37.96±5.60 | 34.72±5.26 | 39.47±5.08 | <0.001 |
| Serum globulin (g/L) | 28.15±5.71 | 28.05±5.82 | 28.20±5.66 | 0.698 |
| Serum calcium (mmol/L) | 2.19±0.68 | 2.11±0.35 | 2.22±0.79 | 0.016 |
| Serum phosphate (mmol/L) | 1.80±0.64 | 1.69±0.64 | 1.85±0.63 | <0.001 |
| Serum kalium (mmol/L) | 4.67±1.24 | 4.55±0.89 | 4.74±1.37 | 0.019 |
| Serum natrium (mmol/L) | 137.80±3.35 | 137.28±3.66 | 138.05±3.16 | 0.001 |
| Serum chlorine (mmol/L) | 98.68±4.31 | 98.85±4.43 | 98.61±4.26 | 0.381 |
| Serum creatinine (mmol/L) | 790.51±331.08 | 708.87±314.26 | 828.71±332.04 | <0.001 |
| BUN (mmol/L) | 19.00 (14.00-25.60) | 18.20 (13.30-25.07) | 19.37 (14.40-25.78) | 0.054 |
| Uric acid (mmol/L) | 391.53±139.38 | 373.28±134.55 | 400.08±140.86 | 0.003 |
| FBG (mmol/L) | 5.80 (4.60-7.90) | 6.20 (4.90-8.06) | 5.52 (4.60-7.70) | 0.002 |
| HbAlc (mg/dl) | 5.30 (4.90-6.00) | 5.33 (4.90-6.18) | 5.30 (4.83-5.93) | 0.083 |
| β2-microglobulin (mg/L) | 27.93 (19.64-36.29) | 28.69 (20.86-37.27) | 27.63 (19.26-35.64) | 0.060 |
| iPTH (pg/ml) | 28.30 (11.60-62.90) | 24.70 (9.66-50.08) | 31.68 (12.61-68.83) | 0.001 |
| pro-BNP (pg/ml) | 11700.00 (3290.00-30000.00) | 26500.00 (12091.00-35000.00) | 7128.39 (1967.50-20052.54) | ≤0.001 |
| hs-CRP (mg/dl) | 7.40 (0.35-33.30) | 12.80 (1.30-40.75) | 4.97 (0.13-29.00) | <0.001 |
| PCT (ng/mL) | 0.61 (0.23-2.51) | 0.61 (0.29-2.69) | 0.61 (0.19-2.44) | 0.024 |

Abbreviations: Data are presented as numbers and percentages, means and standard deviations, or median and quartile ranges. PE, pleural effusion; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; PLT, platelet; RBC, red blood cell; NEUT, neutrophilic granulocyte; LYMP, lymphocyte; MONO, monocyte; Retic, reticulocyte; BUN, blood urea nitrogen; FBG, fasting blood glucose; HbAlc, glycosylated hemoglobin; iPTH, intact parathyroid hormone; pro-BNP, pro-brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; PCT, procalcitonin. Cardiovascular disease included congestive heart failure, angina pectoris, and atherosclerotic heart disease; Cerebrovascular disease included cerebral infarction, hemorrhage, and cerebrovascular stenosis. *For comparisons between PE group and non-PE group.

**Table 2.** Causes and characteristics of PE in hospitalized patients undergoing maintenance hemodialysis (N = 343)

| Diagnosis | Total, n (%) | Bilateral, n (%) |
|---|---|---|
| Heart failure | 267 (77.84) | 219 (63.85)* |
| Non-heart failure | 72 (20.99) | 41 (11.95) |
| Parapneumonic effusion | 38 (11.08) | 24 (7.00) |
| Hypoproteinemia | 11 (3.21) | 10 (2.92) |
| Uremic pleurisy | 9 (2.62) | 4 (1.17) |
| Malignancy | 6 (1.75) | 2 (0.58) |
| Tuberculous pleurisy | 6 (1.75) | 1 (0.29) |
| Hepatic hydrothorax | 2 (0.58) | 0 |
| Unknown | 4 (1.17) | 2 (0.58) |

Abbreviations: Data are presented as numbers and percentages. *$P$<0.05, Heart failure vs non-heart failure.

**Table 3.** Factors for the occurrence of PE in hospitalized patients undergoing maintenance hemodialysis (multivariate logistic regression analysis)

| Variable | OR (95% CI) | $P$ value |
|---|---|---|
| BMI (per 1 kg/m$^2$) | 0.94 (0.90, 0.99) | 0.014 |
| Cardiovascular disease (no = 0; yes = 1) | 1.45 (1.01, 2.08) | 0.047 |
| Clinic-SBP (per 1 mmHg) | 1.10 (1.03, 1.17) | 0.004 |
| Chest tightness (no = 0; yes = 1) | 2.17 (1.50, 3.16) | <0.001 |
| Leg edema (no = 0; yes = 1) | 2.19 (1.53, 3.13) | <0.001 |
| Hemoglobin (per 1 g/L) | 0.98 (0.98, 0.99) | <0.001 |
| Serum albumin (per 1 g/L) | 0.88 (0.85, 0.90) | <0.001 |
| pro-BNP (per 1000 pg/ml) | 1.05 (1.04, 1.07) | <0.001 |

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; pro-BNP, pro-brain natriuretic peptide; OR, odds ratio; CI, confidence interval.

sociated with lower survival probability (HR: 2.15; 95% CI: 1.52-3.04). Regardless of its severity, patients with small, moderate, and large PE had poorer survival than those without PE; the unadjusted HRs were 3.84 (95% CI: 2.81-5.25), 4.96 (95% CI: 3.10-7.94), and 5.82 (95% CI: 3.16-10.73), respectively. Despite the adjustment for other risk factors, these associations remained significant, the adjusted HRs were 2.16 (95% CI: 1.51-3.10), 2.20 (95% CI: 1.31-3.70), and 1.97 (95% CI: 1.02-3.81), respectively (**Table 4**).

## Discussion

Research on PE in hemodialysis patients is limited, though there has been a considerable amount of previous research conducted in the form of case studies. We found that only five studies mentioned the incidence of PE ranging from 7.7% to 45.3% [7-9, 17, 18]. It is possible that these differences were influenced by the timing of evaluation of PE. In the study with the lowest incidence of PE (7.7%), the majority of patients with PE were asymptomatic [7]. On the contrary, another study that reported the highest incidence of PE focused on thoracic problems in symptomatic hemodialysis patients [8]. To our knowledge, ours is the largest study dealing with PE development in patients receiving maintenance hemodialysis. In this retrospective cohort study, we reported the incidence of PE in hospitalized patients undergoing maintenance hemodialysis as 31.9%. The majority of PE patients in our study were asymptomatic, and we found a relatively higher incidence of PE than previous studies, which might be related to the fact that we paid meticulous attention to PE detection by chest CT at our hospital, especially during the Coronavirus 2019 (COVID-19) pandemic. We also found that the PE patients were significantly older, and more likely to have diabetes mellitus, hypertension, and cardiovascular disease. In addition, they had relatively low levels of education, whichmay reflect a relative lack of self-management ability to a certain extent. Hence, it is also clinically beneficial to pay special attention to strengthening public awareness and education for patients undergoing maintenance hemodialysis. Despite the high incidence of PE in patients undergoing maintenance hemodialysis, no detailed evaluation has been conducted in previous studies.

A variety of factors can contribute to the development of PE, including diseases affecting the pleura and systemic disorders [19, 20]. Possible contributors include (1) water and solute retention, congestive heart failure, and other factors that may lead to increased volume load; (2) inflammatory reaction of the pleural cavity and adjacent organs, such as uremic pleurisy, pneumonia, tuberculosis, and so on; (3) hypoproteinemia; (4) malignant PEs; (5) hemothorax; the use of anticoagulants can lead to coagulation disorders during hemodialy-

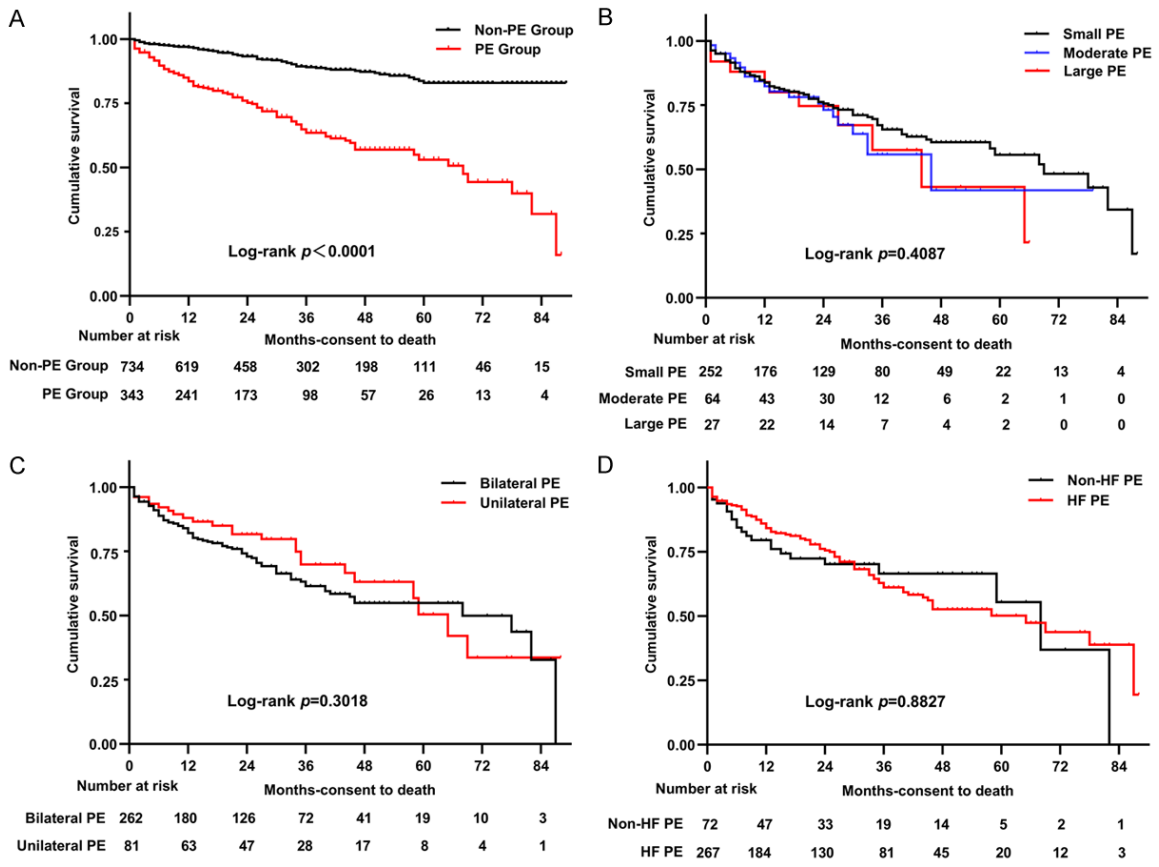


**Figure 2.** Kaplan-Meier survival plots for long-term mortality. A. Curves comparing PE group and non-PE group; B. Curves comparing patients with small PE and those with moderate to large PE; C. Curves comparing unilateral PE with bilateral PE; D. Curves comparing non-HF PE with HF PE. Abbreviations: PE, pleural effusion; HF, heart failure.

**Table 4.** Prognostic value of PE in hospitalized patients undergoing maintenance hemodialysis (Cox regression analysis)

| Variable | n of deaths/n of patients (%) | Unadjusted model | | Adjusted model | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Non-PE | 74/734 (10.22) | 1 (reference) | | 1 (reference) | |
| PE | 118/343 (34.40) | 4.17 (3.12, 5.57) | <0.001 | 2.15 (1.52, 3.04) | <0.001 |
| Small PE | 83/252 (32.94) | 3.84 (2.81, 5.25) | <0.001 | 2.16 (1.51, 3.10) | <0.001 |
| Moderate PE | 23/64 (35.94) | 4.96 (3.10, 7.94) | <0.001 | 2.20 (1.31, 3.70) | 0.003 |
| Large PE | 12/27 (44.44) | 5.82 (3.16, 10.73) | <0.001 | 1.97 (1.02, 3.81) | 0.043 |
| Bilateral PE | 92/262 (35.11) | 4.41 (3.24, 5.98) | <0.001 | 2.45 (1.52, 3.95) | <0.001 |
| Unilateral PE | 26/81 (32.10) | 3.50 (2.24, 5.47) | <0.001 | 2.06 (1.43, 2.97) | <0.001 |

Abbreviations: Adjusted model, adjustment variables include age, BMI, Diabetes mellitus, Cancer, Cardiovascular disease, Clinic-SBP, Dialysis duration, Urine volume, Hemoglobin, serum albumin, pro-BNP. PE, pleural effusion; HR, hazard ratio; CI, confidence interval.

sis; (6) idiopathic: the cause is unknown, and may be associated with a hypercatabolic disease or viral infection [19, 21]. Hemodialysis-related PE is primarily caused by poor fluid management and is mainly treated by the mechanical removal of fluid [22]. The most common cause of PE in this study was congestive heart failure. A similar conclusion was reached in other retrospective observational studies [9, 18]. Our study found that infections were the second most common cause of PE. In fact, researchers have demonstrated that after

restoring renal function by kidney transplantation, the effects of kidney loss on the thymus are not reversed, which leads to a substantially increased risk of susceptibility to infections [23, 24]. Despite reports of an increased risk of tuberculosis [25], we determined that only 1.8% of the patients had tuberculous pleurisy. Fibrinous pleurisy caused by an unknown agent is called uremic pleurisy. Limited study populations may lead to differences in the incidence of uremic pleurisy. In our study, we found an incidence of 2.6%. We also found other causes of PE, but the incidence was very low. It is also worth noting that a greater likelihood of bilateral effusion was seen in PE patients with heart failure than in PE patients without heart failure. A unilateral effusion suggested that the diagnosis was something other than heart failure, most commonly parapneumonic effusion, malignancy, or tuberculous pleurisy; thoracentesis might be performed in patients with unilateral PE to determine the cause [9, 18]. Therefore, this has significant educational value for clinical practice.

Identifying risk factors associated with PE was the most important part of our study. Based on a multivariate logistic regression analysis, we found that cardiovascular disease, clinic-SBP, chest tightness, leg edema, and pro-BNP were independently associated with PE. Among 5,143 patients, 91% of the patients with heart failure had hypertension antedating the development of heart failure, underscoring the fact that in the majority of patients with heart failure, hypertension was a contributing cause, and this is one of the most impactful observations from the Framingham cohort [26]. Another convincing study shows that elevated levels of BP and especially systolic BP are major risk factors for the development of heart failure [27]. We already know that heart failure is the leading cause of PE, and the PE incidence could be reduced most effectively with preventive strategies that aim to control blood pressure earlier and more aggressively. Furthermore, it is important to recognize that patients who develop chest tightness and leg edema in clinical practice, should be diagnosed in a timely manner and prompt treatment should be instituted. Our results show that BMI, hemoglobin, and serum albumin were barrier factors to the occurrence of PE Restoration of hemoglobin and serum albumin should be attempted.

Despite the fact that malignant PE is associated with poor prognosis, only a limited number of studies have examined the correlation between mortality and PE caused by ESRD. In a retrospective study, Kwan et al. reported that PE was associated with a high mortality rate among patients who were undergoing maintenance peritoneal dialysis, with a median survival of one year [28]. Another prospective observational study showed that patients undergoing thoracentesis for PE had high short-term and long-term mortality rates; in particular, bilateral PE was distinctly associated with high mortality [11]. Until now, we have found only one letter to the editor that reported that PE was a risk factor for high mortality among maintenance hemodialysis patients [13]. Our study also reached a similar conclusion; even after adjusting for age, BMI, diabetes mellitus, cancer, cardiovascular disease, clinic-SBP, dialysis duration, urine volume, hemoglobin, serum albumin, and pro-BNP level, the correlation between them was still significant. Statistical correlations were based on the presence or absence of PE, regardless of its size, whether it was bilateral or unilateral, and whether it was caused by heart failure. This view might be different from that of another study that was a prospective study of 356 consecutive unselected patients; it revealed a significant difference in survival between bilateral and unilateral PE [12]. Due to this, our results should be regarded as preliminary and may be a starting point for a prospective study in the future.

### Strengths and limitations

To the best of our knowledge, our study is the largest series dealing with PE in patients undergoing maintenance hemodialysis. Our investigation provides a comprehensive evaluation of the epidemiology, clinical characteristics, risk factors, and prognosis of PE; however, it has five major limitations. First, the study is a retrospective cohort study conducted at a single center; as a result, there are some incomplete data and we were unable to control examinations and treatment, and bias errors are likely to have crept in. Second, we did not fully evaluate dialysis adequacy, including Kt/V, volume status, ultrafiltration rate, the number of intradialytic hypotensive episodes, and inter-dialytic blood pressure. Third, thoracentesis was performed in only a small number of patients,

which might limit the interpretation power of the cause of PE. Fourth, in this retrospective study, we were unable to evaluate the time when PE disappeared and the times of PE relapse, which meant that we cannot provide additional clinical information to better evaluate the prognostic significance of PE. Finally, in order to determine if PE is a marker of treatment change or if more aggressive treatment can improve outcomes after PE diagnosis, further research is needed. A prospective, multicenter, cohort study with larger sample size would be required in the future to overcome these limitations.

## Conclusions

In conclusion, the occurrence of PE in maintenance hemodialysis patients is common. Its presence is a significant adverse prognostic factor for survival. PE is most commonly caused by heart failure. Appropriate treatment in such patients should be directed at support of cardiac function and removal of excess fluid. Simultaneously, positive control of the blood pressure, and restitution of hemoglobin and serum albumin should be attempted. Furthermore, unilateral PE suggested another diagnosis besides heart failure; early thoracentesis should be performed to assist in early diagnosis and prompt treatment.

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## Disclosure of conflict of interest

None.

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