[Thoracic Oncology Original Research]

CHEST

The Impact of Clinically Significant Pleural Effusion on Survival of US Veterans With Cancer, Congestive Heart Failure, and Pneumonia

The Veterans Administration Lung Effusion Study

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BACKGROUND: Previous clinical data suggest that the presence of a pleural effusion is associated with poor survival. However, these studies were limited by either a small sample size or lack of an adequate control group.

RESEARCH QUESTION: What is the impact of pleural effusion on survival in patients hospitalized with an admitting diagnosis of the 3 most common causes of pleural effusion: cancer, congestive heart failure, or pneumonia?

STUDY DESIGN AND METHODS: This is a retrospective analysis of US veterans hospitalized between January 1, 2000 and December 31, 2020. International Classification of Diseases codes were used to identify patients with an admitting diagnosis of congestive heart failure (CHF), pneumonia, or cancer. Patients were dichotomized as having a clinically significant pleural effusion (PE) when a PE drainage was performed or not. The latter group included both patients who had a PE that was not clinically significant (did not require drainage) and those who did not have a PE at the time of index hospitalization (NO-PE). All-cause mortality was compared between the PE and NO-PE cohorts.

RESULTS: We analyzed 34,707 patients in the PE group and 792,217 patients in the NO-PE group. Patients with PE had a significantly higher all-cause mortality compared with patients with no PE. The median survival time was significantly lower in PE group as compared with NO-PE group across all 3 diagnoses, CHF (PE, 1.51 years; 95% CI, 1.40-1.61 vs NO-PE, 3.23 years; 95% CI, 3.21-3.26), cancer (PE, 1.33 years; 95% CI, 1.27-1.39 vs NO-PE, 2.05 years; 95% CI, 2.02-2.08), and pneumonia (PE, 4.27 years; 95% CI, 3.94-4.61 vs NO-PE, 5.11 years; 95% CI, 5.06-5.15). The hazard ratios of all-cause mortality remained unchanged after adjusting for demographics and comorbidities.

INTERPRETATION: The presence of a clinically significant PE was independently associated with higher all-cause mortality in patients with admitting diagnosis of CHF, cancer, and pneumonia. Clinicians and researchers should consider the association of CHF, cancer, and pneumonia with PEs when estimating the prognosis of individual patients and when assessing the survival of longitudinal cohorts. CHEST 2025; ■(■):■-■

KEY WORDS: cancer; congestive heart failure; pleural effusion; pneumonia; survival

ABBREVIATIONS: CHF = congestive heart failure; CPT = Current Procedural Terminology; ICD = International Classification of Diseases; NO-PE = patients who did not have a pleural effusion; PE = pleural effusion; VA = Veteran Health Administration; VALUES = Veterans Administration Lung Effusion Study

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DOI: https://doi.org/10.1016/j.chest.2025.02.003

Take-Home Points

Study Question: What is the impact of clinically significant pleural effusion (PE) on survival in hospitalized patients with an admitting diagnosis of cancer, congestive heart failure (CHF), or pneumonia?

Results: The presence of a clinically significant PE was independently associated with higher all-cause mortality in patients with admitting diagnosis of CHF, cancer, and pneumonia.

Interpretation: Presence of clinically significant PE should be considered as an independent marker for higher all-cause mortality in patients hospitalized with CHF, cancer, and pneumonia diagnoses.

Pleural effusions (PEs) cause significant quality of life impairment, health care utilization, and health care costs.[1] Congestive heart failure (CHF), cancer, and pneumonia are the most common causes of PE in United States,[2] and there is a rising trend for these 3 conditions to be associated with PE.[1] Although both malignant and nonmalignant PE have been associated with poor survival,[3,4] these studies were limited by a small sample size or lack of a control group. We performed a large retrospective study from the national Veterans Health Administration (VA) database [5] to compare the survival of patients hospitalized with or without clinically significant PEs who were admitted with a diagnosis of cancer, CHF, and pneumonia—the Veterans Administration Lung Effusion Study (VALUES). We adjusted our analyses for numerous comorbidities.

Study Design and Methods

This study was approved by the Stratton VA Medical Center (Albany, NY) institutional review board (IRB#1694150). This was a retrospective study of preexisting data obtained for medical purposes.

VA informatics[6] were used to identify patients who were hospitalized at VA hospitals across the United States between January 1, 2000 and December 31, 2020 with an admitting diagnosis of CHF, pneumonia, and malignancy, using International Classification of Diseases (ICD), 9th Revision, and ICD, 10th Revision, codes (e-Table 1). We excluded all patients with more than 1 of these 3 admitting diagnoses such that only patients with 1 of these 3 admitting diagnoses were analyzed. A patient was defined as having a clinically significant PE if a pleural drainage procedure was performed. Patients with a clinically significant PE were identified by either (a) Current Procedural Terminology (CPT) procedure codes; (b) ICD procedure codes (e-Table 2)[1]; or (c) the presence of a specific laboratory test result concerning pleural fluid in their medical record such as pleural fluid lactate dehydrogenase or pleural fluid protein level. Patients were dichotomized as having clinically significant PE or not. The latter group included both patients who had a PE that was not clinically significant (did not require drainage) and those who did not have a PE at the time of index hospitalization (NO-PE).

To determine all-cause mortality from the patients' initial hospitalization, the patients were followed up until death or the date of their most recent VA clinic visit. We obtained comorbidity data on all patients concerning all components of the Charlson Comorbidity Index.[5]

Statistical Analysis

The primary study outcome was all-cause mortality. Unadjusted all-cause mortality was compared between PE and NO-PE cohorts using Kaplan-Meier estimators, and these curves were compared using log-rank tests. We then performed an adjusted analysis using Cox proportional hazard models, taking into account the demographics (age, sex, race) and all components of the Charlson Comorbidity Index, which included the following comorbidities: cirrhosis, mild liver disease, dementia, chronic pulmonary disease, coronary artery disease, peripheral vascular disease, chronic kidney disease, CHF, pneumonia, diabetes mellitus, peptic ulcer disease, AIDS, cerebral vascular disease, myocardial infarction, and cancer. These comorbidities were identified using ICD codes. We assumed 0.05 type I error rate for all analyses. We assessed the goodness-of-fit of the Cox models by inspection of Schoenfeld residuals and the concordance index. The R language (version 4.3.1) was used for all statistical analyses.

Results

We identified 1,064,827 patients with an admitting diagnosis of cancer, CHF, or pneumonia (Fig 1). Of those, 237,799 were excluded from the analysis because of having more than 1 admitting diagnosis of cancer, CHF, or pneumonia, yielding 827,028 patients with only 1 of these 3 diagnoses. A total of 34,713 had a PE during the index hospitalization, and 792,315 had NO-PE. We

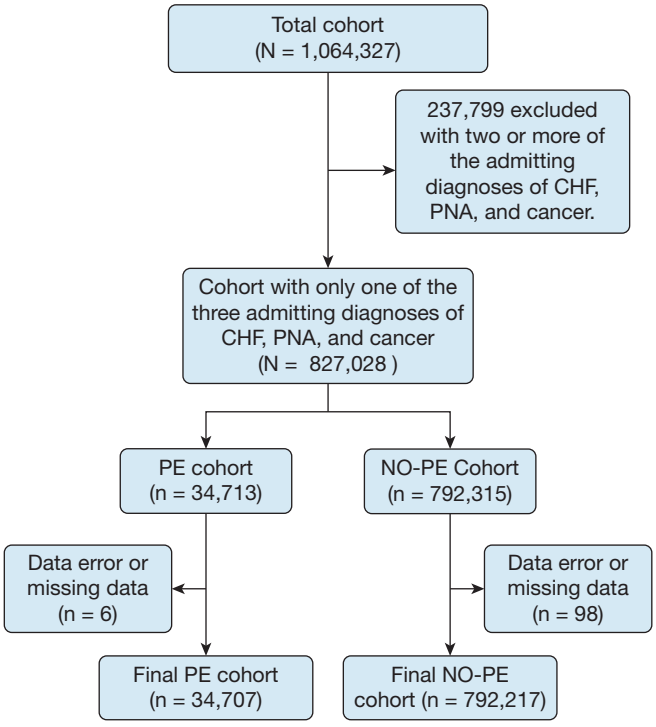

Figure 1 – *STROBE diagram. CHF = congestive heart failure; NO-PE = patients who did not have a pleural effusion; PE = pleural effusion; PNA = pneumonia; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology.*

excluded 6 patients with a PE from the analysis because of data errors or missing data, leaving 34,707 patients in the final PE group. In the 792,315 patients with a single diagnosis in the NO-PE group, we excluded 98 patients with data errors or missing data, leaving 792,217 patients in the final comparison NO-PE cohort.

Table 1 describes the demographic characteristics and comorbidities of the patients. The cohort was male-predominant (97%). Although there were statistically significant differences in some of the demographic characteristics and comorbidities between the PE and NO-PE groups, the magnitude of these differences was minor. In addition, because the proportion of patients with missing data was small in the PE cohort (n = 6; 0.002%) and in the NO-PE cohort (n = 98; 0.001%), these missing data did not appreciably affect our results.

Figure 2 shows the Kaplan-Meier survival curves of unadjusted all-cause mortality for patients admitted with a diagnosis of CHF with PE vs NO-PE. There was a statistically significant difference in the Kaplan-Meier surival estimates between CHF with PE vs NO-PE groups ($P < .0001$). The median survival time was significantly lower in patients with CHF with a PE as compared with NO-PE (PE, 1.51 years; 95% CI, 1.40-1.61 vs NO-PE, 3.23 years; 95% CI, 3.21-3.26). The median follow-up time from hospitalization was 12.7 years (95% CI, 12.0-13.8) for the CHF PE group and 10.2 years (95% CI, 10.1-10.3) for the CHF NO-PE (e-Table 3). The survival curves of the CHF PE group and the CHF NO-PE group continued to separate for approximately 1 year after the index hospitalization.

Figure 3 shows the Kaplan-Meier survival curves of unadjusted all-cause mortality for patients admitted with a diagnosis of cancer with PE or NO-PE. There was a statistically significant difference in the Kaplan-Meier surival estimates between cancer with PE vs NO-PE ($P < .0001$). Median survival time was significantly lower in cancer patients with a PE as compared with NO-PE (PE, 1.33 years; 95% CI, 1.27-1.39 vs NO-PE, 2.05 years; 95% CI, 2.02-2.08). The median follow-up time from hospitalization was 8.4 years (95% CI, 8.2-8.6) for the cancer PE group and 12.3 years (95% CI, 12.3-12.4) for the cancer NO-PE group (e-Table 3). The survival curves of cancer PE group and cancer NO-PE group continue to separate for 3 years after index hospitalization.

Figure 4 shows the Kaplan-Meier survival curves of all-cause unadjusted mortality for patients admitted with a diagnosis of pneumonia with PE vs NO-PE. There was a statistically significant difference in the Kaplan-Meier

TABLE 1] Comparison of Demographics and Clinical Characteristics

Characteristic	Heart Failure			Cancer			Pneumonia		
	No Effusion (n = 213,227)	Effusion (n = 5,156)	SMD	No Effusion (n = 403,042)	Effusion (n = 23,638)	SMD	No Effusion (n = 175,948)	Effusion (n = 5,913)	SMD
Age-y, mean (SD)	70.7 (11.8)	73.0 (11.1)	0.21[a]	66.9 (10.8)	67.8 (9.4)	0.90[a]	68.0 (14.0)	64.9 (13.5)	0.23[a]
Male sex	97.6	97.6	0	96.4	96.2	0.01	95.3	97.1	0.11[a]
Race									
White	62.4	66.6	0.09	63.1	66.3	0.07	67.6	64.9	0.06
Black	20.4	11	0.3[a]	17.4	13.6	0.11[a]	15.7	15.2	0.01
Other	1.4	1.1	0.03	1.4	1.2	0.02	1.5	1.6	0.01
Unknown	15.8	21.3	0.14[a]	18.1	18.9	0.02	15.3	18.4	0.08
Comorbidity									
Liver cirrhosis	2.2	2.6	0.03	3.5	2.6	0.06	2.6	4.1	0.08
Mild liver disease	10.9	11.5	0.02	14.6	13.3	0.04	11.6	14.2	0.07
Dementia	25.7	19.2	0.17[a]	19.5	24.2	0.11[a]	29.2	19.7	0.24[a]
Chronic pulmonary disease	52.7	50	0.05	36.9	56.5	0.40[a]	58.8	48.5	0.21[a]
Coronary artery disease	67	63.7	0.07	27.4	32.7	0.11[a]	37.8	31.1	0.15[a]
Peripheral vascular disease	39	40.7	0.03	19.9	26.6	0.15[a]	27.2	23.6	0.08
Chronic kidney disease	41.6	40.5	0.02	20.1	19.9	0.01	25.2	21.2	0.1
Connective tissue disease	4.7	5.3	0.03	3.2	3.8	0.03	5.6	5.2	0.02
Heart failure	NA	NA	NA	8.5	9.8	0.04	17.5	15.5	0.05
Pneumonia	21.9	25.6	0.08	11.6	17.8	0.16[a]	NA	NA	NA
Cancer	16.1	17.9	0.05	NA	NA	NA	17.8	16.9	0.03
Diabetes (types 1 and 2)	56.5	56.7	0	30.7	30.6	0	36.9	33.2	0.08
Peptic ulcer disease	7.9	8.6	0.03	6.8	7.3	0.02	8.6	8.6	0
Metastatic cancer	1.1	1.3	0.02	20.4	18.4	0.05	1.6	1.7	0.01
Hemiplegia	4	3.8	0.01	3.2	2.6	0.04	6.6	6	0.03
AIDS	0.6	0.6	0	0.8	0.7	0.01	2.4	2	0.03
Cardiovascular disease	29.9	31.2	0.03	16.4	18.8	0.06	2.6	2.1	0.13[a]
Myocardial infarction	30.9	27.2	0.08	7.8	8.9	0.04	12.6	10.2	0.08

[a]SMD > .1 is suggestive of imbalance of the corresponding between the cohort.The only continuous variable is age, which is reported as means and SDs. The remaining variables are categorical, which are reported as percentages. A standardized mean difference of less than 0.1 suggests balance in the corresponding variable between the cohorts, values beyond that threshold are denoted in the table in red highlight. NA = not applicable; SMD = standardized mean difference.

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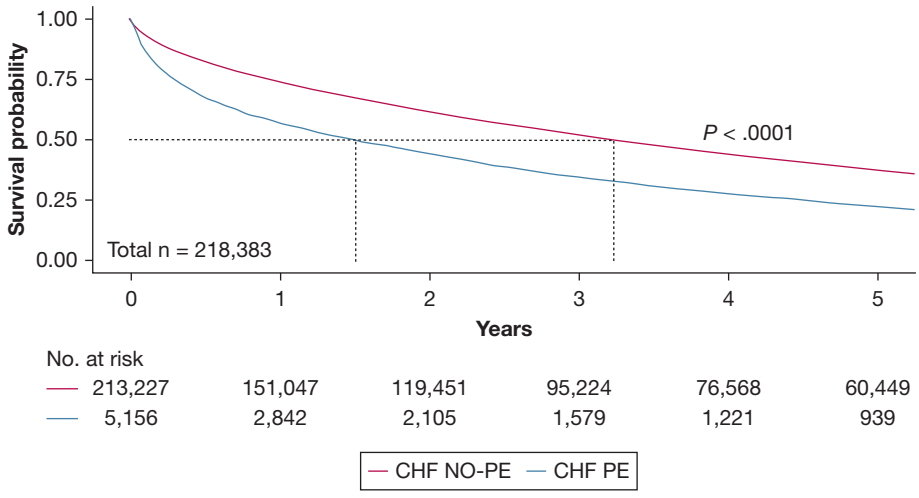

Figure 2 – *Kaplan-Meier curves comparing unadjusted all-cause mortality of patients with congestive heart failure with pleural effusion and in whom a pleural effusion drainage was not performed. The dotted line represents median survival time. CHF = congestive heart failure; NO-PE = patients who did not have a pleural effusion; PE = pleural effusion.*

surival estimates between pneumonia with PE vs NO-PE ($P < .0001$). The median survival time was significantly lower in patients with pneumonia with PE as compared with NO-PE (PE, 4.27 years; 95% CI, 3.94-4.61 vs NO-PE, 5.11 years, 95% CI, 5.06-5.15). The median follow-up time from hospitalization for the pneumonia PE group was 15.1 years (95% CI, 14.7-15.5) and 12.6 years (95% CI, 12.5-12.6) for the pneumonia NO-PE group (e-Table 3). The survival curves of the pneumonia PE group and pneumonia NO-PE group separated only during the initial few months after hospitalization.

We also adjusted hazard ratios (HRs) for all-cause mortality among all 3 cohorts and found no substantial differences in results (ie,HRs remained significantly > 1 and comparable in magnitude after adjustment). Hospitalized patients with an admission diagnosis of CHF and a PE had a higher all-cause mortality as compared with NO-PE (Fig 5: unadjusted HR for all-cause mortality: 1.55; 95% CI, 1.51-1.60; and the HR for all-cause mortality adjusted for age, sex, and all Charlson index comorbidities: 1.40 (95% CI, 1.36-1.45). Furthermore, all-cause mortality was higher in patients with cancer and PE as compared with cancer with NO-PE (Fig 5: The unadjusted HR for all-cause mortality was 1.23 [95% CI,1.21-1.25], and the HR for all-cause mortality adjusted for age, sex, and comorbidities was 1.15 [95% CI, 1.13-1.17]). Similar results hold true for pneumonia and PE compared with pneumonia and NO-PE (Fig 5: The unadjusted HR for all-cause

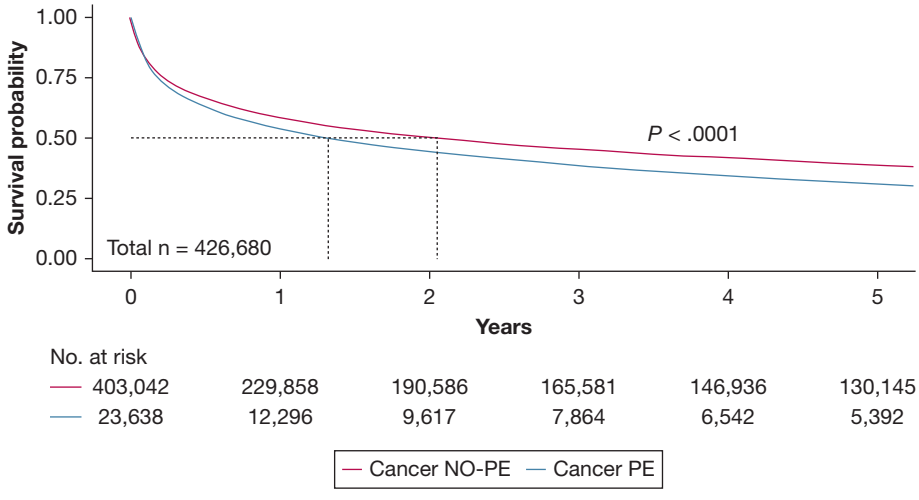

Figure 3 – *Kaplan-Meier curves comparing unadjusted all-cause mortality of patients with cancer with pleural effusion and in whom a pleural effusion drainage was not performed. The dotted line represents median survival time. NO-PE = no pleural effusion; PE = pleural effusion.*

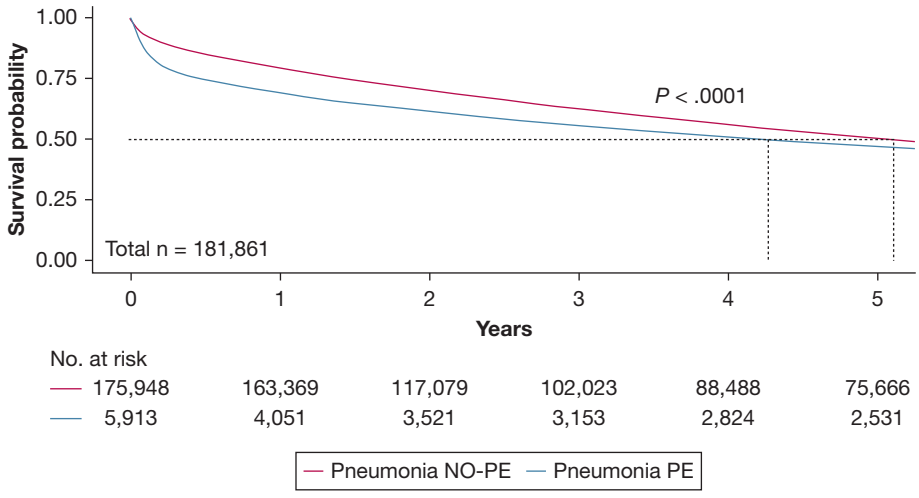

Figure 4 – *Kaplan-Meier curves comparing unadjusted all-cause mortality of patients with pneumonia with pleural effusion and in whom a pleural effusion drainage was not. A dotted line represents median survival time. NO-PE = no pleural effusion; PE = pleural effusion.*

mortality was 1.07 [95% CI, 1.03-1.10] and the HR for all-cause mortality adjusted for age, sex, and comorbidities was 1.30 [95% CI, 1.26-1.34]).

Discussion

In our cohort of approximately 1 million hospitalized veterans with a single admitting diagnosis of CHF, cancer, or pneumonia, the presence of clinically significant PE was independently associated with higher all-cause mortality. This association persisted even after adjusting for demographics and for all the comorbidities in the Charlson Comorbidity Index. This suggests that a significant PE in these patients may represent an independent biomarker for poor outcome.

Previous studies have demonstrated that PEs are associated with decreased survival in patients with CHF, cancer, and pneumonia.[4,6–13] However, our study has several strengths compared with previous studies. First, we analyzed a significantly larger cohort. Second, we adjusted for possible cofounders that allow for a more accurate assessment of the impact of a PE on mortality. Finally, we incorporated longitudinal follow-up data spanning more than a decade, allowing determination of both short-term and long-term mortality, which, to our knowledge, has not been done in previous studies.

We speculate that a major reason for the decreased survival of patients with these 3 admitting diagnoses is that the presence of a PE signifies that normal pleural clearance mechanisms have been overwhelmed, suggesting severe disease. We believe that this is the case in terms of CHF-associated effusions. In patients with cancer, a PE may signify tumor invasion of either the pleural space, pulmonary lymphatics, or the pulmonary vasculature.[14–16] All of these phenomena may suggest an aggressive tumor or an advanced tumor stage. PEs associated with pneumonia may result from direct extension of infection into the pleural space or via hematogenous spread; both events suggest extensive

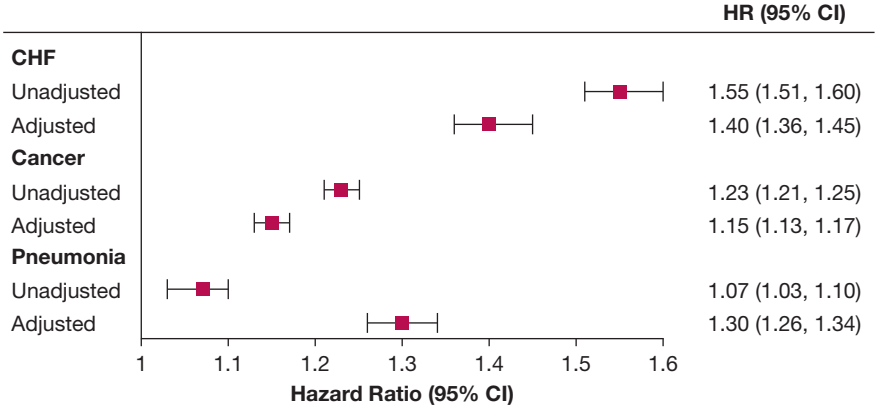

Figure 5 – *Forest plot showing the HRs for the unadjusted and adjusted analyses. The reference group is those in whom a pleural effusion drainage was not performed; thus, the pleural effusion cohort had a significantly increased hazard compared with the NO-PE cohort. HR = hazard ratio; NO-PE = no pleural effusion; PE = pleural effusion.*

spread of infection.[17] Pleural infection is often associated with loculations which compromises effective drainage.[18] In addition, an infected pleural space may serve as a sanctuary for microorganisms where antibiotics penetrate poorly.

For cancer diagnoses, the survival curves of the PE and NO-PE groups continued to diverge after their index hospitalization, which may be because patients with cancer-related PE likely had metastatic cancer. The survival curve of CHF-related PE also continues to separate for at least 1 year. This suggests that the mortality differences are probably not strictly related to the initial hospitalization but reflect poorer health status and severity of organ dysfunction in patients with CHF. There was only initial separation of the survival curve in the pneumonia cohort, which suggests that pneumonia-related PE does not have a long-term effect on mortality.

This study has several potential limitations. First, we assumed that these significant PEs were caused by the admitting diagnoses, which was probably inaccurate in a small percentage of patients. Second, ICD and CPT codes were used to identify study patients, which may not be completely accurate because of coding errors and misclassification bias. Third, because this study was based on the ICD and CPT codes, we were not able to adjust for the disease-specific severity indices. Fourth, some patients in the NO-PE group may have had effusions that were not drained because of futility (eg, a cancer-related PE in a patient receiving palliative care), nondrainage interventions (eg, a heart failure-related effusion that was treated with diuretics), or drainage of the effusion was deemed of no clinical benefit. We chose clinically significant PEs (effusions that were drained) because (1) there may be inaccuracies surrounding the coding of PE by physicians and (2) it was not possible to review and verify several hundred thousand images to confirm the presence or absence of a PE. Although it is possible that including undrained PEs in the NO-PE group might have created a misclassification bias, it is unlikely that this limitation appreciably changed the significant findings of this large data set. Finally, our study was done using a VA cohort, which was male-predominant and might limit the generalizability of study results.

Interpretation

In summary, our analysis shows that in hospitalized veterans with admission diagnosis of CHF, pneumonia, or cancer, the presence of clinically significant PE was independently associated with higher mortality. Our adjusted analyses suggest that a significant PE may be an independent biomarker for poor long-term outcome for these 3 diagnoses. The presence of a PE should be considered when analyzing survival of cohorts with these diagnoses.

Funding/Support

This material is the result of work supported with resources and the use of facilities at the Stratton VAMC, Albany, NY. D. E. G. is an employee of the US Department of Veterans Affairs, and his opinions expressed in this paper are those of the authors' and do not represent the views of the Department of Veterans Affairs or the US Government. This work was supported using resources and facilities at the VA Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-457. Support for VA/CMS Data provided by the Department of Veterans Affairs, VA Health Services Research and Development Service, VA Information Resource Center (Project Numbers SDR 02-237 and 98-004).

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: A. C. reports royalties for writing UpToDate chapters. K. H. reports speaker fee for Verona pharmaceutical and is on the advisory board for Sanofi/Regeneron. M. A. J. is a consultant for Priovant, Sparrow Pharmaceuticals, Merck, aTyr Pharmaceuticals, and Xentria Pharmaceuticals. None declared (D. G.).

Acknowledgments

Author contributions: A. C. is the guarantor of the paper and takes responsibility for the integrity of the work, from inception to published article. D. E. G. is the data scientist and has contributed to the study design, data collection, data analysis, and interpretation. K. H. has contributed toward writing, editing, and data display. M. A. J. is the senior author and has contributed to the study design, writing, editing, and revision of the manuscript.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Additional information: The e-Tables are available online under "Supplementary Data."

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