The effect of frailty on mortality and hospital admission in patients with benign pleural disease in Wales: a cohort study

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Summary

Background Pleural disease is common, representing 5% of the acute medical workload, and its incidence is rising, partly due to the ageing population. Frailty is an important feature and little is known about disease progression in patients with frailty and pleural disease. We aimed to examine the effect of frailty on mortality and other relevant outcomes in patients diagnosed with pleural disease.

Methods In this cohort study in Wales, the national Secure Anonymised Information Linkage databank was used to identify a cohort of individuals diagnosed with non-malignant pleural disease between Jan 1, 2005, and March 1, 2023, who were not known to have left Wales. Frailty was assessed at diagnosis of pleural disease using an electronic Frailty Index. The primary outcome was time from diagnosis to all-cause mortality for all patients. Data were analysed using multilevel mixed-effects Cox proportional hazards regression adjusting for the prespecified covariates of age, sex, Welsh Index of Multiple Deprivation quintile, smoking status, comorbidity, and subtype of pleural disease.

Findings 54 566 individuals were included in the final sample (median age 66 years [IQR 47–77]; 26 477 [48·5%] were female and 28 089 [51·5%] were male). By the end of the study period, 25 698 (47·1%) participants had died, with a median follow-up of 1·0 years (IQR 0·2–3·6). There was an association between frailty and all-cause mortality, which increased as frailty worsened. Compared with fit individuals, there was increasing mortality for those with mild frailty (adjusted hazard ratio 1·11 [95% CI 1·08–1·15]; p<0·0001), moderate frailty (1·25 [1·20–1·31]; p<0·0001), and severe frailty (1·36 [1·28–1·44]; p<0·0001).

Interpretation Independent of age and comorbidities, frailty status at diagnosis of pleural disease appeared to be useful as a prognostic indicator. Patients with moderate or severe frailty had a rapid decline in health. Future patients should be assessed for frailty at the time of diagnosis of pleural disease and might benefit from optimised care and advance care planning.

Funding Cardiff University's Wellcome Trust iTPA funding award.

Lancet Healthy Longev 2024; 5: e534–41
https://doi.org/10.1016/S2666-7568(24)00114-4

See Comment page e508

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Introduction

Pleural disease is a collection of disorders of the pleura (including pleural infection, pleural thickening, pleural malignancy, and pneumothorax), and its incidence has risen substantially over the past decade.[1,2] An estimated 1·5 million new pleural effusions are identified annually in the USA and 250 000 in the UK, with many due to malignancy or infection.[1,2] Hospital admissions relating to pleural infection in the UK have increased from 4447 in 2008 to more than 7000 in 2017.[3] In the UK, the cost of pleural procedures to the National Health Service (NHS) in 2019–22 was £13·4 million.[4] Studies exploring the epidemiology of pleural disease show that it is more common among adults aged 65 years and older, and is often associated with other long-term health conditions, such as cardiac failure, cancer, chronic obstructive pulmonary disease (COPD), or lung fibrosis.[5]

Frailty was first recognised as an important feature in respiratory medicine in 2016.[6] A 2023 task force of the European Respiratory Society identified patients with frailty as being under-represented within respiratory medicine and called for greater research to both understand the prognostic role and explain the mechanism of action.[7] Despite these initiatives, little evidence has been generated to support management of frail patients with pleural disease.

Ageing is seen as the leading prognostic feature of pleural disease; however, frailty might offer greater understanding of disease progression and appropriate treatment options. Although there is overlap between chronological age, biological age, and frailty, there is a distinction between them. Frailty is a syndrome characterised by reduced physiological capacity and an increased vulnerability to physiological stressors, even very minor ones.[8] However, although there is overlap between frailty and chronic comorbid diseases, after controlling for demographic characteristics and underlying disease, frailty is associated with worse clinical outcomes, across medical specialties.[9]

Frailty can be assessed using existing primary care records, which can be used to establish a patient's level of frailty at a particular point in time. This has been shown to be useful for informing a patient's prognosis at the point of

Research in context

Evidence before this study

We did a systematic review of the literature using four databases (PubMed, Web of Science, Cochrane Library, and Embase) from database inception to Oct 25, 2022, assessing the evidence base for associations between frailty and mortality or outcomes relating to hospital admissions among patients with pleural disease. Our search terms were "frailty" AND ("pleural effusions" OR "pleural disease" OR "mesothelioma" OR "pneumothorax"), with no language restrictions. No relevant studies were found for patients with pleural disease and frailty, identifying a clear gap in the available evidence base.

Added value of this study

In our study of more than 50 000 cases of pleural disease in a national patient database from 2005 to 2023, we were able to associate increasing levels of frailty with key health outcomes including mortality and hospital admissions. We provide evidence that moderate and severe levels of frailty result in a rapid decline in health among patients with pleural disease, independent of age and comorbidities.

Implications of all the available evidence

These findings support frailty assessment for patients with pleural disease at time of presentation. A patient's frailty status should be considered at presentation to help tailor their diagnostic pathway, clinical management, and advance care planning.

diagnosis, and for providing appropriate treatment plans.[10] The electronic Frailty Index (eFI) is one such tool that uses data from existing records to assess the presence of 36 deficits and thereafter derives a frailty score.[11] Patients classified as frail using the eFI have been found to show poorer health outcomes.[12] The Secure Anonymised Information Linkage (SAIL) databank is a large data source,[13] which holds the primary care records for 86% of the Welsh population. The eFI was developed and validated within SAIL.[14]

There are scarce data describing the link between frailty and pleural disease.[15] Recognising frailty at diagnosis of pleural disease might improve clinicians' understanding of disease progression and prognosis. The primary aim of this study was to evaluate the prognostic utility of frailty at diagnosis of pleural disease for all-cause mortality within a national sample of patients identified via the SAIL databank. Secondary aims were to assess the importance of frailty for other clinical outcomes, including pleural disease-related mortality, admission to hospital, length of hospital stay, and re-admission within 90 days.

Methods

Study design

This cohort study included data from a national population sample in Wales. The protocol and statistical analysis plan were drafted using the King's Clinical Trials Unit standard operating procedure and published on ResearchSquare on May 30, 2023.

For the **protocol and statistical analysis plan** see https://doi.org/10.21203/rs.3.rs-2971853/v1

Data sources

The national SAIL databank holds the health records of approximately 86% of the Welsh population. Wales had a population of 3·1 million in 2022.[16] SAIL anonymously links primary and secondary care data with the Office for National Statistics. Within SAIL, the following datasets were linked: Welsh Longitudinal General Practice Dataset (WLGP); Patient Episode Dataset for Wales (PEDW); Outpatient Database for Wales; Emergency Department Dataset; Welsh Demographic Service Dataset; and Annual District Death Extract (ADDE). The SAIL databank hosts an Information Governance Review Panel, which provides independent guidance and advice on information governance policies, procedures, and processes. The panel review all proposals to ensure that they are appropriate and in the public interest.

This databank was used to extract all diagnoses of non-malignant pleural disease between Jan 1, 2005, and March 1, 2023, from any of the general practice, outpatient, or hospital datasets. Pleural disease diagnosis was detected by ICD-10 codes (J86 and J90–J94) of pleural effusion, pleural plaque, pyothorax, pneumothorax, and other diseases of pleura or by NHS Read Codes (H50, H51, H51z, H52, and H410.00) via the WLGP and PEDW datasets. Although pleural plaques are typically suggestive of benign asymptomatic disease, a proportion of patients have extensive plaques in their costophrenic angles, which cause pain on breathing. Additionally, plaques that occupy more than 25% of each hemithorax can cause a restrictive deficit. We therefore chose to include pleural plaques. Patients who were known to have left Wales at the end of the study were excluded (fewer than ten; number not defined to preserve anonymity, as per SAIL regulations). No data on the race or ethnicity of the participants were available. Data on sex were extracted from WLGP and PEDW datasets.

Procedures and outcomes

The primary outcome was time to all-cause mortality, measured using the time from the date of pleural disease diagnosis to the date of death. The remaining patients who did not have a date of death (in any of the databases) were assumed to be alive and were censored at the end of the study period (March 1, 2023).

Secondary outcomes were time to pleural disease-related mortality, where patients were censored at death if they died of any other cause (cause of death was extracted from the ADDE death certificate registry); time to first all-cause

hospital admission after diagnosis; time to pleural disease-related hospital admission, where patients were censored at death if this occurred before, or on the day of, hospital admission, and only hospital stays that were longer than 24 h and where the patient did not die on admission were included; length of stay (time to discharge) of first all-cause and pleural disease-related hospital admissions after diagnosis (patients who died on admission were excluded from these analyses); and any re-admission within 90 days of the first all-cause and pleural disease-related admission. Hospital admission data were extracted from the PEDW database.

Frailty was calculated at the date of first diagnosis of pleural disease using the eFI. The eFI estimates frailty based on the presence of 36 deficits within routinely collected health-care data.[11] The eFI was calculated within SAIL and categorised as not frail (0 to 0·12), mildly frail (>0·12 to 0·24), moderately frail (>0·24 to 0·36), or severely frail (>0·36).

Baseline covariates were sex at birth; age in years; socioeconomic status (measured using the Welsh Index of Multiple Deprivation [WIMD], which is the Welsh Government's measure of deprivation for areas in Wales across domains of income, education, health, employment, housing, services, and community safety); presence of COPD; smoking status (current, former, or never); presence of heart failure; Charlson Comorbidity Index (CCI; 0, 1, 2, 3, 4, or ≥5 comorbidities); and specific pleural disease diagnosis (J90/J91 pleural effusion, J86 pyothorax, J92 pleural plaque, J93 pneumothorax, or J94 other pleural conditions).

Statistical analysis

To detect a hazard ratio (HR) of 1·25 of mortality between those who had mild frailty and those who were not frail using a type I error of 0·0125 (three comparisons) and 90% power, at least 1700 participants (or 1200 events) would be needed.

The effects of frailty (fit, mild, moderate, or severe) on time to all-cause mortality using mixed-effects Cox proportional hazards regression were assessed. There was adjustment for age (<65 years, 65–74 years, 75–84 years, or ≥85 years), sex (male *vs* female), WIMD quintile, smoking status (current, former, or never), COPD presence, heart failure presence, CCI (0 *vs* 1, 2, 3, 4, or ≥5), and pleural

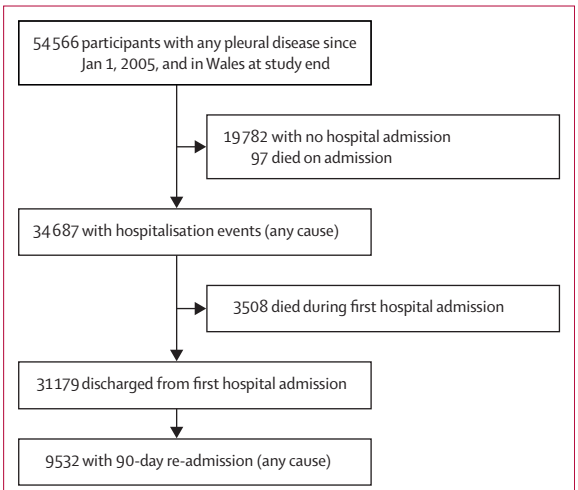


Figure 1: **Flowchart showing cohort size for each analysis**

	Alive (n=28 868)	Died (n=25 698)	Total (n=54 566)
Frailty			
Fit	18 650 (64·6%)	8344 (32·5%)	26 994 (49·5%)
Mild	7555 (26·2%)	9038 (35·2%)	16 593 (30·4%)
Moderate	2189 (7·6%)	6086 (23·7%)	8275 (15·2%)
Severe	474 (1·6%)	2230 (8·7%)	2704 (5·0%)
Age, years			
<65	20 972 (72·6%)	5325 (20·7%)	26 297 (48·2%)
65–74	4330 (15·0%)	6727 (26·2%)	11 057 (20·3%)
75–84	2786 (9·7%)	8442 (32·9%)	11 228 (20·6%)
≥85	780 (2·7%)	5204 (20·3%)	5984 (11·0%)
Sex			
Male	13 647 (47·3%)	14 442 (56·2%)	28 089 (51·5%)
Female	15 221 (52·7%)	11 256 (43·8%)	26 477 (48·5%)
Smoking status			
Current	6097 (21·1%)	3433 (13·4%)	9530 (17·5%)
Former	9986 (34·6%)	10 940 (42·6%)	20 926 (38·3%)
Never	12 785 (44·3%)	11 325 (44·1%)	24 110 (44·2%)
WIMD			
1	7074 (24·5%)	5532 (21·5%)	12 606 (23·1%)
2	6245 (21·6%)	5583 (21·7%)	11 828 (21·7%)
3	5979 (20·7%)	5503 (21·4%)	11 482 (21·0%)
4	4888 (16·9%)	4781 (18·6%)	9669 (17·7%)
5	4671 (16·2%)	4293 (16·7%)	8964 (16·4%)
Missing	0	0	17 (<0·1%)
COPD			
No	25 433 (88·1%)	19 667 (76·5%)	45 100 (82·7%)
Yes	3435 (11·9%)	6031 (23·5%)	9466 (17·3%)
Cardiac failure			
No	27 127 (94·0%)	20 246 (78·8%)	47 373 (86·8%)
Yes	1741 (6·0%)	5452 (21·2%)	7193 (13·2%)
Diagnosis			
J90/J91 pleural effusion	21 659 (75·0%)	20 975 (81·6%)	42 634 (78·1%)
J86 pyothorax	1208 (4·2%)	822 (3·2%)	2030 (3·7%)
J92 pleural plaque	978 (3·4%)	895 (3·5%)	1873 (3·4%)
J93 pneumothorax	4825 (16·7%)	2688 (10·5%)	7513 (13·8%)
J94 other pleural conditions	198 (0·7%)	318 (1·2%)	516 (0·9%)
CCI			
0	10 324 (35·8%)	4219 (16·4%)	14 543 (26·7%)
1	2009 (7·0%)	1311 (5·1%)	3320 (6·1%)
2	2659 (9·2%)	2904 (11·3%)	5563 (10·2%)
3	5885 (20·4%)	3634 (14·1%)	9519 (17·4%)
4	1980 (6·9%)	2593 (10·1%)	4573 (8·4%)
≥5	6011 (20·8%)	11 037 (42·9%)	17 048 (31·2%)

Data are n (%). CCI=Charlson Comorbidity Index. COPD=chronic obstructive pulmonary disease. WIMD=Welsh Index of Multiple Deprivation.

Table 1: **Participant characteristics by mortality status**

disease diagnosis (J90/J91, J86, J92, J93, or J94). The site code of the diagnosing hospital was included as a random effect in the model (to allow convergence of the models, sites with ≤20 cases were combined). Crude and adjusted HRs with their associated 95% CIs and p values were calculated. The baseline proportional hazards assumption was assessed visually using log–log plots, adjusting for the covariates, and there were no violations across all outcomes. Survival rates, stratified by frailty status, were visualised using Kaplan–Meier survival plots.

The secondary outcomes were analysed using a time-to-event approach consistent with the primary outcome. The effect of frailty on 90-day hospital re-admission was analysed using multilevel logistic regression, adjusting for covariates consistent with the time-to-event analyses, and also including diagnosing hospital site as a random effect. Missing data were explored for pattern missingness.

Our post-hoc subgroup analyses examined the effects of frailty (fit *vs* mild to severe) on time to all-cause mortality, and time to first any-cause hospitalisation within each demographic and clinical subgroup of patients, using mixed-effect Cox proportional hazards regression consistent with the primary time-to-event analyses.

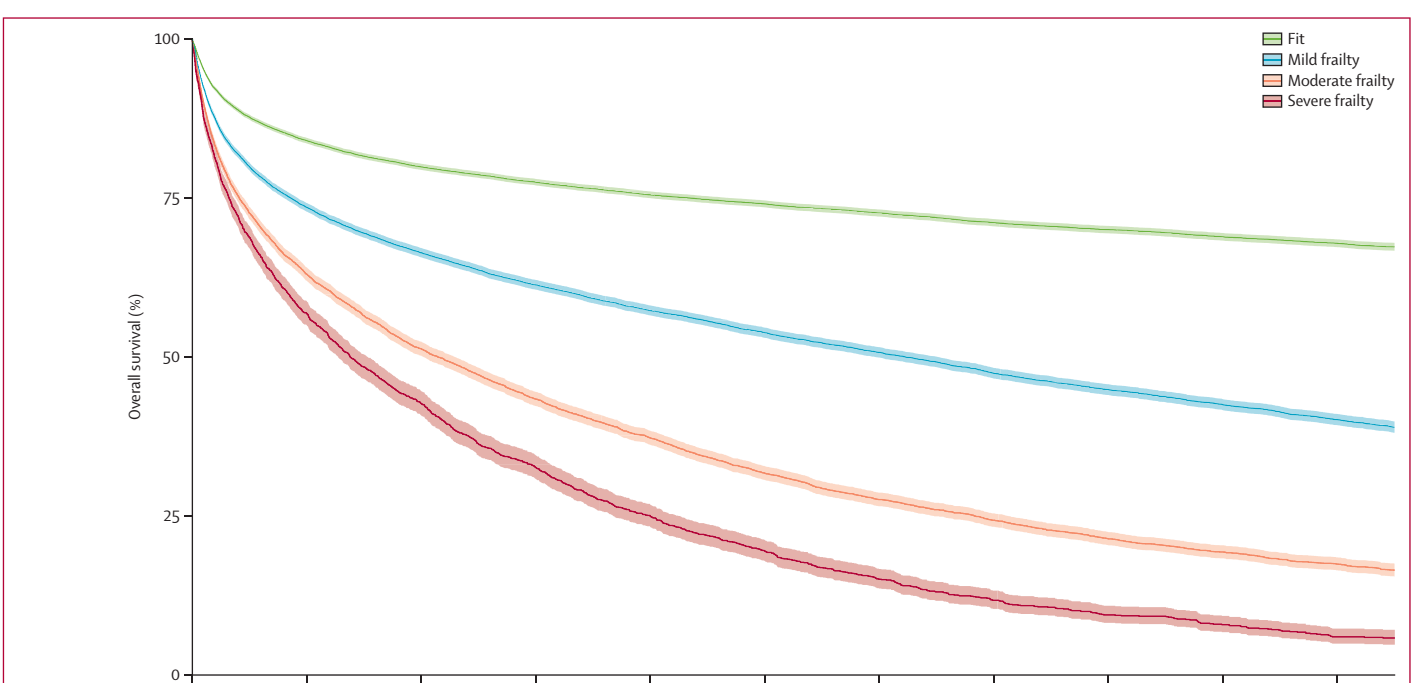
We carried out a post-hoc sensitivity analysis to check the primary findings were consistent after excluding any participant who had a malignancy (J84 interstitial lung disease, C45 mesothelioma, C34 lung cancer, or I27 primary pulmonary hypertension) during follow-up. All analyses were conducted in Stata version 18, and all plots were produced in R version 4.1.3.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The data were first accessed on July 27, 2023. The final sample comprised 54 566 individuals who had been diagnosed with pleural disease between Jan 1, 2005, and March 1, 2023 (figure 1). Median age was 66 years (IQR 47–77); 26 477 (48·5%) participants were female and 28 089 (51·5%) were male (table 1). By the end of the study period, 25 698 (47·1%) participants had died, with a median follow-up of 1·0 years (IQR 0·2–3·6). The median follow-up for those who survived was 8·0 years (IQR 3·8–12·6). Cause of death was available for 25 193 individuals. Of these,



Number at risk (number censored)

Fit	26 994 (0)	21 698 (1023)	19 717 (1968)	18 392 (2710)	16 834 (3819)	15 441 (4894)	14 021 (6026)	12 646 (7119)	11 472 (8108)	10 316 (9087)	9134 (10 123)
Mild frailty	16 593 (0)	11 564 (691)	9847 (1318)	8671 (1761)	7523 (2363)	6509 (2933)	5612 (3473)	4785 (3954)	4138 (4353)	3513 (4770)	2952 (5149)
Moderate frailty	8275 (0)	4921 (335)	3745 (624)	2992 (817)	2376 (1029)	1852 (1212)	1481 (1351)	1173 (1495)	935 (1600)	758 (1690)	597 (1781)
Severe frailty	2704 (0)	1434 (120)	1003 (206)	709 (271)	508 (310)	371 (338)	257 (372)	183 (392)	139 (401)	104 (415)	72 (423)

Figure 2: **Kaplan–Meier plot showing overall survival by electronic Frailty Index categories (n=54 566)**

392 (1·6%) had pleural disease stated as a cause of death, with a median follow-up of 62 days (IQR 18–305). In terms of missing data, 17 (<0·1%) participants had missing deprivation indices at the start of the study period; 3225 (5·9%) participants had missing or unknown smoking status, and these participants were imputed as never smokers.

26 994 (49·5%) participants were classified as fit on the eFI, with 16 593 (30·4%) classified as mildly frail, 8275 (15·2%) as moderately frail, and 2704 (5·0%) as severely frail (table 1). The median survival for those with mild frailty was 6·2 years (95% CI 6·0–6·5), compared with 2·1 years (2·0–2·3) for those with moderate frailty, and 1·4 years (1·3–1·5) for those with severe frailty (figure 2). 18 650 (69·1%) of 26 994 without frailty (ie, classified as fit) remained alive at the end of follow-up. 7555 (45·5%) of 16 593 with mild frailty, 2189 (15·2%) of 8275 with moderate frailty, and 474 (5·0%) of 2704 with severe frailty remained alive at the end of follow-up.

There was an association between frailty and all-cause mortality, which increased as frailty worsened. Compared with fit individuals, there was an increasing risk of mortality for those with mild, moderate, and severe frailty (table 2; figure 2). Age appeared to be a key confounder of this association (table 2), but the direction of the effects of frailty remained consistent before and after adjustment.

Frailty was associated with pleural disease-related mortality. Compared with fit individuals, there was increasing risk of mortality for those with moderate and severe frailty (appendix p 2).

There was an increasing association with worsening frailty and time to first all-cause hospitalisation. The median time to hospitalisation was 4·3 years (95% CI 4·1–4·5) for fit participants, 1·3 years (1·3–1·4) for those with mild frailty, 0·6 years (0·6–0·7) for those with moderate frailty, and 0·4 years (0·4–0·5) for those with severe frailty (appendix p 8). Compared with fit individuals, there was increasing risk of hospitalisation for those with mild, moderate, and severe frailty (table 3; appendix p 8). However, frailty was not associated with hospitalisation for pleural disease (appendix p 3).

There was an association between frailty and first hospital admission time to discharge. Compared with fit individuals, there was a longer time to discharge for those with mild, moderate, and severe frailty (appendix pp 4, 9). However, there was no significant association between frailty and length of first pleural disease-related hospital stay (appendix p 5).

There was an association between frailty and 90-day any-cause hospital re-admission. Compared with fit individuals, there was increased odds of re-admission for those with moderate or severe frailty but not mild frailty (appendix p 6). However, frailty was not independently associated with the presence of a pleural disease-related hospital re-admission within 90 days (appendix p 7).

In our subgroup analyses, frailty was associated with increased mortality and hospitalisation for almost all demographic and clinical subgroups of patients (appendix pp 10–11). Notable exceptions were for the older age categories (75–84 years and ≥85 years) in both risk of mortality and hospitalisation, as well as the 65–74-year age group, those in the 4th and 5th quintiles of the WIMD, and those with one or two comorbidities for risk of mortality. Frailty was associated with reduced mortality in those with no other comorbidities (appendix p 10). For hospitalisation, frailty had a larger effect size in men than women and although an association between frailty and mortality was seen in men, it was not seen in women (appendix pp 10–11).

See Online for appendix

	HR (95% CI)	p value	aHR (95% CI)	p value
Frailty				
Fit	1 (ref)	..	1 (ref)	..
Mild	2·23 (2·16–2·30)	<0·0001	1·11 (1·08–1·15)	<0·0001
Moderate	3·63 (3·50–3·75)	<0·0001	1·25 (1·20–1·31)	<0·0001
Severe	4·76 (4·53–4·99)	<0·0001	1·36 (1·28–1·44)	<0·0001
Age, years				
<65	1 (ref)	..	1 (ref)	..
65–74	4·05 (3·90–4·20)	<0·0001	3·50 (3·36–3·64)	<0·0001
75–84	6·24 (6·02–6·47)	<0·0001	5·07 (4·87–5·29)	<0·0001
≥85	10·11 (9·70–10·53)	<0·0001	7·93 (7·56–8·31)	<0·0001
Sex				
Male	1 (ref)	..	1 (ref)	..
Female	0·94 (0·91–0·96)	<0·0001	0·89 (0·86–0·91)	<0·0001
Smoking status				
Current	0·75 (0·72–0·78)	<0·0001	1·27 (1·22–1·33)	<0·0001
Former	1·12 (1·09–1·15)	<0·0001	1·03 (1·00–1·06)	0·062
Never	1 (ref)	..	1 (ref)	..
WIMD				
1	0·91 (0·88–0·95)	<0·0001	1·11 (1·07–1·16)	<0·0001
2	0·99 (0·95–1·03)	0·61	1·08 (1·03–1·12)	<0·0001
3	1·00 (0·95–1·04)	0·83	1·06 (1·02–1·11)	0·0061
4	1·02 (0·98–1·07)	0·33	1·06 (1·01–1·11)	0·0087
5	1 (ref)	..	1 (ref)	..
COPD				
No	1 (ref)	..	1 (ref)	..
Yes	1·40 (1·36–1·44)	<0·0001	1·01 (0·98–1·04)	0·48
Cardiac failure				
No	1 (ref)	..	1 (ref)	..
Yes	1·89 (1·84–1·95)	<0·0001	0·92 (0·89–0·95)	<0·0001
Diagnosis				
J90/J91 pleural effusion	1 (ref)	..	1 (ref)	..
J86 pyothorax	0·45 (0·42–0·49)	<0·0001	0·71 (0·66–0·76)	<0·0001
J92 pleural plaque	0·89 (0·83–0·95)	0·0005	0·58 (0·54–0·63)	<0·0001
J93 pneumothorax	0·42 (0·41–0·44)	<0·0001	0·68 (0·65–0·71)	<0·0001
J94 other pleural conditions	0·70 (0·62–0·78)	<0·0001	0·87 (0·78–0·98)	0·016
CCI				
0	1 (ref)	..	1 (ref)	..
1	1·61 (1·52–1·72)	<0·0001	1·12 (1·05–1·20)	0·0004
2	2·35 (2·24–2·46)	<0·0001	1·56 (1·49–1·64)	<0·0001
3	1·47 (1·41–1·54)	<0·0001	1·26 (1·21–1·32)	<0·0001
4	2·55 (2·43–2·68)	<0·0001	1·44 (1·37–1·52)	<0·0001
≥5	3·40 (3·28–3·53)	<0·0001	1·58 (1·51–1·65)	<0·0001

aHR=adjusted HR. CCI=Charlson Comorbidity Index. COPD=chronic obstructive pulmonary disease. HR=hazard ratio. WIMD=Welsh Index of Multiple Deprivation.

Table 2: **Time to all-cause mortality (n=54 566; 25 698 events)**

	HR (95% CI)	p value	aHR (95% CI)	p value
Frailty				
Fit	1 (ref)	..	1 (ref)	..
Mild	1·77 (1·73–1·82)	<0·0001	1·25 (1·21–1·29)	<0·0001
Moderate	2·42 (2·35–2·50)	<0·0001	1·38 (1·33–1·44)	<0·0001
Severe	2·97 (2·83–3·12)	<0·0001	1·53 (1·44–1·62)	<0·0001
Age, years				
<65	1 (ref)	..	1 (ref)	..
65–74	1·93 (1·88–1·99)	<0·0001	1·57 (1·52–1·62)	<0·0001
75–84	2·40 (2·33–2·47)	<0·0001	1·76 (1·70–1·82)	<0·0001
≥85	2·59 (2·50–2·69)	<0·0001	1·79 (1·71–1·87)	<0·0001
Sex				
Male	1 (ref)	..	1 (ref)	..
Female	1·02 (1·00–1·04)	0·054	0·98 (0·96–1·00)	0·094
Smoking status				
Current	0·91 (0·88–0·94)	<0·0001	1·06 (1·02–1·09)	0·0013
Former	1·17 (1·15–1·20)	<0·0001	1·05 (1·02–1·07)	0·0004
Never	1 (ref)	..	1 (ref)	..
WIMD				
1	1·02 (0·98–1·06)	0·33	1·09 (1·05–1·13)	<0·0001
2	1·04 (1·00–1·08)	0·053	1·06 (1·02–1·09)	0·0043
3	1·02 (0·98–1·06)	0·31	1·03 (1·00–1·07)	0·081
4	1·01 (0·97–1·05)	0·66	1·02 (0·98–1·06)	0·38
5	1 (ref)	..	1 (ref)	..
COPD				
No	1 (ref)	..	1 (ref)	..
Yes	1·47 (1·43–1·51)	<0·0001	1·14 (1·11–1·18)	<0·0001
Cardiac failure				
No	1 (ref)	..	1 (ref)	..
Yes	1·89 (1·84–1·95)	<0·0001	1·22 (1·19–1·26)	<0·0001
Diagnosis				
J90/J91 pleural effusion	1 (ref)	..	1 (ref)	..
J86 pyothorax	0·60 (0·56–0·63)	<0·0001	0·76 (0·71–0·81)	<0·0001
J92 pleural plaque	0·89 (0·84–0·94)	<0·0001	0·69 (0·65–0·74)	<0·0001
J93 pneumothorax	0·63 (0·61–0·66)	<0·0001	0·81 (0·79–0·84)	<0·0001
J94 other pleural conditions	0·79 (0·71–0·88)	<0·0001	0·89 (0·80–0·98)	0·024
CCI				
0	1 (ref)	..	1 (ref)	..
1	1·49 (1·42–1·56)	<0·0001	1·20 (1·14–1·26)	<0·0001
2	1·69 (1·63–1·76)	<0·0001	1·34 (1·29–1·40)	<0·0001
3	1·34 (1·30–1·39)	<0·0001	1·19 (1·15–1·23)	<0·0001
4	1·89 (1·81–1·97)	<0·0001	1·30 (1·24–1·36)	<0·0001
≥5	2·25 (2·19–2·32)	<0·0001	1·34 (1·30–1·40)	<0·0001

aHR=adjusted HR. CCI=Charlson Comorbidity Index. COPD=chronic obstructive pulmonary disease. HR=hazard ratio. WIMD=Welsh Index of Multiple Deprivation.

Table 3: **Time to first all-cause hospital admission (n=54 566; 34 687 events)**

In the post-hoc sensitivity analysis, we found no difference in the findings for the association between frailty and all-cause mortality after excluding participants who had malignancy during follow-up.

Discussion

In this national cohort study of 54 566 patients with pleural disease, we found that increased frailty at diagnosis was linked to poorer health outcomes (including increased all-cause mortality, hospital admission, re-admission, and time to hospital discharge) after accounting for patient age, type of disease, and other key comorbidities.

Our large-scale, national data linkage cohort study adds to the limited evidence base evaluating the role of frailty in pleural disease. One previous study found that frailty was associated with mortality in patients with pleural disease,[17] and similar findings have been reported in patients with other respiratory diseases.[18] A systematic review showed that people with frailty had more than a four-fold chance of dying from COPD[19] and another showed patients with frailty and interstitial lung disease were twice as likely to die.[15] However, in all of the previous studies, the degree of frailty was not considered. We found that as frailty increased from mild, to moderate, to severe, there was a consistent worsening of outcomes, which was seen in all-cause mortality, pleural disease-specific mortality, length of first hospital stay, and 90-day re-admission to hospital. This study highlights the increased risk of mortality in patients with frailty and pleural disease. Improving clinicians' understanding of this increased risk will enable them to devise patient-centred management strategies that prioritise symptomatic care in those who are unlikely to benefit from invasive management, or in those with more severe frailty with other comorbidities. Hence, these findings could have implications for the clinical management of this vulnerable patient group. Management is highly dependent on the underlying cause of pleural disease. Investigation of the cause alone, with aspiration and thoracoscopic or surgical biopsies, is invasive and not without risk, with many patients requiring multiple aspirations or biopsies before obtaining a diagnosis or undergoing definitive management of their disease.[20] Being frail might prohibit more invasive procedures, including surgical intervention. For many patients, there might be a substantial long-term burden associated with disease management, including repeated aspirations, further scans and outpatient appointments, or treatment of an underlying malignancy, which might not be appropriate for frail patients with a shorter life expectancy.

One common explanation offered for the effects of frailty in other disease areas is that frail patients have so little physiological reserve left after an acute incident that they are unable to return to their baseline functional level, resulting in a loss of independence and eventually mortality.[21] In other words, they are unable to deal with the increased burden of developing a pleural disease, which is often a clinically significant illness. Furthermore, reduced physical activity and sarcopenia, which are associated with frailty,[22] have been found to be important prognostic factors in pleural disease. Sarcopenia is associated with poorer outcomes in patients with malignant pleural disease related to lung cancer,[23,24] and in patients with pleural effusion.[25] Reduced physical activity has been implicated in pulmonary dysfunction and is linked to the development of sarcopenia.[26] Although frailty and sarcopenia are separate entities, there is considerable overlap, especially in terms of the physical characteristics, so it is likely that many of these patients would be

sarcopenic, as well as frail.[26] Another potentially important biomarker that might provide mechanistic evidence for the association between frailty and poorer outcomes in patients with pleural disease is chronic systemic inflammation. Frailty has been frequently and robustly associated with increased levels of C-reactive protein,[27] and inflammatory responses in the pleura are responsible for the development of pleural effusion and pleural scarring.[28]

We also found that frailty was associated with poorer hospital outcomes among patients with pleural disease, including increased hospitalisation, increased hospital re-admission, and longer time to hospital discharge. These findings, although not established in patients with pleural disease until now, are consistent with the wider literature on frailty for patients with other respiratory conditions and in medicine more widely. For example, frailty was associated with increased risk of re-admission in patients with COPD[6] and following lung resection for cancer.[29] Other authors have reported that one in four frail patients are re-admitted within a month of index hospitalisation for a variety of causes.[2]

This study used an eFI, which relies on general practice data and is a simple and easy to use accumulative deficit model. Assessing and reporting frailty in people with pleural disease should be best clinical practice because it would allow clinicians and allied health-care professionals to optimise patient care for patients with pleural disease through shared decision making and advanced care planning. This is especially relevant for the most severely frail, where time to mortality was 1·4 years and time to first hospital admission was 0·4 years. Additionally, as with most diseases, people in the lowest socioeconomic groups were disproportionally affected. The impact of these findings could be to inform policy and guideline development for frail patients diagnosed with pleural disease. These findings support clinical practice to reverse and slow increasing frailty with interventions such as exercise, nutrition, and the replacement of vitamin D.[26,30]

This was a national cohort study following an a priori protocol published before accessing the data. The cohort included the majority of residents of Wales diagnosed with pleural disease between 2005 and 2023. The Welsh population is broadly reflective of the wider UK population and those of western Europe but might not reflect those of the wider European context. It is possible that frail individuals are more susceptible to pleural disease owing to factors such as decreased levels of physical activity, sarcopenia,[22] chronic inflammation,[27] or occupation.[20,27] Data on these factors were not accessible for participants during this study; however, almost half of our cohort were classified as fit, suggesting that these cases of pleural disease were not caused by frailty. It is worth noting that although the eFI has been shown to have good convergent validity,[31] it also has a tendency to overestimate frailty compared with other frailty measures.[32] Additionally, the eFI has only been validated in populations aged 65 years and older,[11] whereas our sample had a median age of 66 years, and thus a large number of people younger than 65 years. Nonetheless, the results of this study emphasise the importance of frailty assessment, and regardless of the method used to assess frailty, it would seem prudent to advocate for the routine use of frailty assessment in patients with benign pleural disease. Although we focused on benign pleural disease in this study, it is possible that on further investigation, a proportion of patients might have had malignancy as the underlying cause. However, excluding patients with malignancy during follow-up did not affect the primary findings. We were unable to account for the effects of ethnicity on frailty and related outcomes. Ethnicity has been found to be associated with frailty in the UK and worldwide;[33] however, these are likely to be complex associations, and studies have been unable to distinguish the causes of such differences (eg, migration and social deprivation).

Further limitations of note were that we considered pleural disease as a single disease group, and these findings only offer external validity for participants with a pleural disease diagnosis and not those without a pleural disease diagnosis. Pleural diseases are individual conditions that are likely to behave in different ways, and future prospective cohort studies are required for individual pleural disease diagnoses and their respective control groups. However, the purpose of this study was to elucidate the general association between people living with frailty and pleural disease, as pleural disease was one of the last remaining areas where frailty had not been established as a significant disease predictor. This research will allow for further study of frailty in this area, including how different pleural diseases affect people living with frailty.

Being frail at the time of diagnosis with a pleural disease increases a patient's risk of mortality, hospital admission, and re-admission. These findings support the introduction of shared decision making and consideration of advance care planning at diagnosis for moderately to severely frail patients.

Contributors

JH conceived the idea. JH, BC, and NM received funding for the project. AV carried out the systematic review of the literature. AV, BC, JH, and NM developed the protocol. BC developed the statistical analysis plan, which was reviewed by EB, JH, and NM. BC and RS analysed and interpreted the data. BC and RS authored the first draft of the manuscript. BC and RS accessed and verified the underlying data, and BC verified the findings. Under SAIL restrictions, only two authors (RS and BC) were able to access the dataset. All authors reviewed and approved the manuscript. JH is the guarantor. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

These data were analysed within the SAIL secure data repository and are available there. We do not have access or ability to share the data outside of the SAIL secure data repository. Researchers wishing to access SAIL databases should apply to do so via the SAIL website.

For the **SAIL website** see https://saildatabank.com

Acknowledgments

Funding for the project was secured by JH through Cardiff University's Wellcome Trust iTPA funding award (Access to Expertise award 214601/

Z/18/Z). BC is part funded by the National Institute for Health and Care Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. NM is part funded by the NIHR Biomedical Research Centre at University of Bristol. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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