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Benign pleural disease and the impact of frailty at diagnosis on mortality and admission to hospital in Wales: a cohort study

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Research in Context

Evidence available before this study

A systematic review using four databases (PubMed, Web of Science, Cochrane Library, and Embase) from inception to 25th October 2022, assessing the evidence base for associations between patients with pleural disease (PD) who were living with frailty. Our search terms were: frailty AND (pleural effusions OR pleural disease OR mesothelioma OR pneumothorax). Eligible studies included those pertaining to individuals with PD and frailty, where frailty was associated with mortality and/or outcomes related to hospital admissions. No relevant studies were found for patients with PD and frailty, identifying a clear gap in the available evidence base.

Added value of this study

This study demonstrates the clear disease trajectory for patients living with frailty at diagnosis of PD. Median survival for moderately and severely frail patients was 2.1 and 1.4 years following a PD diagnosis. The median time to hospitalisation was 4.3, 1.3, 0.6 and 0.4 years (for fit, mildly, moderately and severely frail patients).

Implications of all the available evidence

These findings support frailty assessment for patients with PD 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.

Summary

Background

Pleural disease (PD) 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 PD. We aimed to examine the effect of frailty on mortality and other relevant outcomes in patients diagnosed with PD.

Methods

The national secure anonymised information linkage databank was used to identify a cohort of individuals diagnosed with PD. Frailty was assessed at diagnosis of PD using an electronic frailty index. The primary outcome was time from diagnosis to all-cause mortality. Data were analysed using multilevel mixed-effects cox proportional hazards regression adjusting for pre-specified covariates age, deprivation, smoking status, comorbidity, and subtype of PD.

Findings

In Wales 54,566 individuals were diagnosed with PD between 1st January 2005 and 1st March 2023 (median age 66 years; 49% female). By the end of the study, 25,698 (47.1%) had died, with a median follow-up time of 1.0 years (IQR 0.2-3.6). There was an increasing association between worsening frailty and all-cause mortality, as well as hospitalisation, and 90-day hospital readmission. Compared to fit individuals, there was increasing mortality for those with mild (aHR=1.11, 95%CI 1.08-1.15), moderate (aHR=1.25, 95%CI 1.20-1.31), and severe frailty (aHR=1.36, 95%CI 1.28-1.44).

Interpretation

Independent of age and comorbidities, frailty status at diagnosis of PD exhibited utility as a prognostic indicator. Patients that were moderately (or severely frail) experienced a rapid decline in health. Future patients should be assessed for frailty at the time of diagnosis of PD and may benefit from optimised care and advance care planning.

Introduction

Pleural disease (PD) represents a collection of disorders of the pleura (including pleural infection, pleural thickening, pleural malignancy and pneumothorax), and its incidence has risen dramatically over the last decade (1, 2). There are an estimated 1.5 million new pleural effusions identified annually in the US 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 to over 7000 between 2008 and 2017(3). In the UK, the cost of pleural procedures to the NHS in 2019/2022 was £13.4 million (5). Studies exploring the epidemiology of PD demonstrate that it is more common amongst older adults, and often associated with other long-term health conditions, such as cardiac failure, cancer, chronic obstructive pulmonary disease or lung fibrosis (6).

Frailty was first recognised as an important feature in respiratory medicine in 2016 (7) and a recent task force of the European Respiratory Society identified patients with frailty as under-represented within respiratory medicine and called for greater research to understand both the prognostic role and explain the mechanism of action (8). Despite these initiatives, little evidence has been generated to support management of frail patients with PD.

At present, ageing is seen as the leading prognostic feature, whereas frailty may offer greater understanding of disease progression and appropriate treatment options. Whilst there is overlap between chronological age, biological age and frailty, there is a distinction between them. Frailty is a syndrome characterized by reduced physiological capacity and an increased vulnerability to physiological stressors, even very minor ones (10). However, whilst 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 (11).

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 diagnosis, and for providing appropriate treatment plans (12). The Electronic Frailty Index (eFI) is one such tool that uses data from existing records to assess the presence of approximately 30 conditions/deficits and thereafter derives a frailty score (13). Patients classified as frail using the eFI have been found to show poorer health outcomes (14). The Secure Anonymised Information Linkage (SAIL) Databank is a large data source (15), which holds the primary care records for 86% of the Welsh population. The eFI was developed and validated within SAIL (16).

Currently, there are no data describing the link between frailty and PD (17). Recognising frailty at diagnosis of PD may 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 PD on all-cause mortality within a national sample of patients identified via the SAIL databank. Secondary aims were to assess the importance of frailty on other clinical outcomes including: PD related mortality; admission to hospital; length of stay and readmission within 90 days.

Methods

Study design

The protocol and statistical analysis plan was drafted using the King's Clinical Trials Unit (KCTU) Standard operating procedure and published on ResearchSquare on May 30th, 2023 (https://doi.org/10.21203/rs.3.rs-2971853/v1). Funding for the project was secured through Cardiff University's Wellcome Trust iTPA funding award [Access to Expertise (A2E) award - 214601/Z/18/Z]

Data Sources

The national secure anonymised information linkage (SAIL) Databank holds the health records of approximately 86% of the Welsh population. Wales had a population of 3.1 million in 2022 (18). SAIL anonymously links primary and secondary care data with the Office for National Statistics (ONS). 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. They 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 PD between 1st January 2005 and 1st March 2023. PD diagnosis was detected by ICD-10 code (J86, J90-J94) of "Pleural effusion", "Pleural plaque"[1], "Pyothorax", "Pneumothorax", and "Other diseases of pleura" or NHS Read Codes (H50, H51, H51z, H52, and H410.00) via the WLGP and PEDW datasets.

[1] Although pleural plaques are typically suggestive of benign asymptomatic disease, a proportion have extensive plaques in their costophrenic angles, which cause pain on breathing. In addition, plaques that occupy greater than 25% of each hemithorax can cause a restrictive deficit. For these reasons we chose to include them.

Primary outcome

The primary outcome was all-cause mortality, measured using the time-to-mortality from the date of PD diagnosis. A small number of patients who were known to have left Wales at the end of the study period were excluded from the cohort (fewer than 10; number not defined to preserve anonymity, as per SAIL regulations). The remaining patients who did not have a date of death (in any of the databases) were assumed alive and were censored at the end of the study period (1st March 2023) (Figure 1).

Secondary outcomes

Secondary outcomes were: time to PD-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 PD-related hospital admission, where patients were censored at death if this occurred prior to, or on the day of, hospital admission, and only hospital stays that were longer than 24 hours, and where the patient did not die on admission were included; length of stay (time to discharge) of first all-cause, and PD-related hospital admissions after diagnosis (patients who died on admission were excluded from these analyses [N=96]; see Figure 1); and presence of any readmission within 90 days of the first all-cause and PD-related admission.

Exposures

The electronic frailty index (eFI) estimates frailty based on the presence of 36 deficits within routinely-collected healthcare data (see Clegg et al., 2016 for further details (13)). This was calculated within SAIL and categorised as not frail (0 to 0.12), mildly frail (>0.12-0.24), moderately frail (>0.24-0.36) and severely frail (>0.36). Frailty was calculated at the date of first diagnosis of PD using the eFI.

Baseline covariates were: sex at birth; age in years; socio-economic 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 chronic obstructive pulmonary disease (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 PD diagnosis (J90/J91 Pleural effusion, J86 Pyothorax, J92 pleural plaque, J93 pneumothorax, J94 other pleural conditions).

Sample size

To detect an HR=1.25 of mortality between those that were mildly frail and those that were not frail using a type-1 error=0.0125 (three comparisons) and 90% power at least 1700 participants (or 1200 events) would be needed.

Data Analysis

The effects of frailty (fit, mild, moderate, severe) on time to all-cause mortality using mixed-effects Cox proportional hazards regression were assessed. There was adjustment for age (under 65, 65-74, 75-84, and 85 and over), sex (male vs female), WIMD quintile, smoking status (current, former, never), COPD presence, heart failure presence, CCI (0 vs 1, 2, 3, 4, or >=5), and PD diagnosis (J90/J91, J86, J92, J93, J94). Site code of diagnosing hospital was included as a random effect in the model[2]. Crude and adjusted Hazard Ratios (aHR) with their associated 95% confidence intervals and p-values, are presented. 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 readmission 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 was explored for pattern missingness.

Our supplementary subgroup analyses examined the effects of frailty (fit vs mild-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.

Finally, we carried out a post-hoc sensitivity analysis to check the primary findings were consistent after excluding any participant that experienced a malignancy (J84 interstitial lung disease, C45 mesothelioma, C34 lung cancer and/or I27 primary pulmonary hypertension) during follow-up. All analyses were conducted in Stata v18, and all plots were produced in R.

Role of the funding source

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

[2] To allow convergence of the models, sites with 20 or fewer cases were combined

Results

The data were first accessed on 27th July 2023. The final sample comprised 54,566 individuals who had been diagnosed with PD between 1st January 2005 and 1st March 2023, with a median age of 66 years (IQR 47-77), of which 48.5% were women (N=26,477; see Table 1). By the end of the study period (1st March, 2023), N=25,698 (47.1%) had died, with a median follow-up time of 1.0 years (IQR 0.2-3.6 years). The median follow-up time for those who survived was 8.0 years (IQR 3.8-12.6). Cause of death was available for N=25,193 individuals. Of these, 392 (1.6%) had PD stated as a cause of death, with a follow-up time of 62 days (IQR 18-305). In terms of missing data, 17 cases had missing deprivation indices at the start of the study period. 3,225 cases (5.9%) had missing or unknown smoking status, which were imputed as never smokers.

Approximately half of the sample was classified as fit on the electronic frailty index (N=26,994, 49.5%), with 30.4% classified as mildly frail, 15.2% as moderately frail, and 5.0% as severely frail (Table 1). The median survival time for those with mild frailty was 6.2 years (95%CI 6.0-6.5), compared to 2.1 years (95%CI 2.0-2.3) for those with moderate frailty, and 1.4 years (95%CI 1.3-1.5) for those with severe frailty (Figure 2). 69% of those without frailty (i.e., classified as fit) remained alive at the end of follow-up. The median time to hospitalisation was 4.3 years (95%CI 4.1-4.5) for fit, 1.3 years (95% CI 1.3-1.4) for mildly frail, 0.6 years (95%CI 0.6-0.7) for moderately frail, and 0.4 years (95%CI 0.4-0.5) for severely frail patients (Figure S1).

There was an association between frailty and all-cause mortality, which increased as frailty worsened. Compared to fit individuals, there was an increasing risk of mortality for those with mild (aHR=1.11, 95%CI 1.08-1.15), moderate (aHR=1.25, 95%CI 1.20 -1.31), and severe frailty (aHR=1.36, 95%CI 1.28-1.44,) (Table 2; Figure 2). Age appeared to be a key confounder of this association (see Table 2), but the direction of the effects of frailty remained consistent before and after adjustment. We found no difference in the findings after excluding participants who experienced malignancy during follow-up.

Frailty was associated with PD-related mortality. Compared to fit individuals, there was increasing risk of mortality for those with moderate (aHR=1.49, 95%CI 1.03-2.14), and severe frailty (aHR=1.75, 95%CI 1.12-2.72) (Table S1, Supplementary Appendix p. 2).

There was also an increasing association with worsening frailty and time to first any-cause hospitalisation. Compared to fit individuals, there was increasing risk of hospitalisation for those

with mild (aHR=1.25, 95%CI 1.21-1.29), moderate (aHR=1.38, 95%CI 1.33-1.44), and severe frailty (aHR=1.53, 95%CI 1.44-1.62) (Table 3; Figure S1, Supplementary Appendix p. 8). However, frailty was not associated with hospitalisation for PD (Table S2, Supplementary Appendix p. 3).

There was an association between frailty and first hospital admission time to discharge. Compared to fit individuals there was a longer time to discharge for those with mild (aHR=0.95 95%CI 0.92-0.98), moderate (aHR=0.90, 95%CI 0.86-0.93), and severe frailty (aHR=0.86, 95%CI 0.81-0.91) (Table S3, Supplementary Appendix p. 4; Figure S2, Supplementary Appendix p. 9). However, there was no significant association between frailty and length of first PD-related hospital stay (Table S4, Supplementary Appendix p. 5).

There was an association between frailty and 90-day any-cause hospital readmission. Compared to fit individuals, there was increased odds of readmission for those with mild (aOR= 1.06, 95%CI 0.99-1.13), moderate (aOR= 1.20, 95%CI 1.10-1.31), and severe frailty (aOR=1.27, 95%CI 1.11-1.44) (Table S5, Supplementary Appendix p. 6). However, frailty was not independently associated with the presence of a PD-related hospital readmission within 90 days (Table S6, Supplementary Appendix p. 7).

In our subgroup analyses, frailty was associated with increased mortality and hospitalisation for almost all demographic and clinical subgroups of patients (see Figures S3 and S4, Supplementary Appendix p. 10-11). Notable exceptions were for the older age categories (75-84, and 85 and over) in both risk of mortality and hospitalisation, as well as the 65-74 age group, those in the 4th and 5th quintiles of the WIMD, and those with one or two comorbidities for mortality. Frailty was associated with reduced mortality in those with no other comorbidities. For both mortality and hospitalisation, frailty appeared to have a larger effect in men than women (see Figures S3 and S4, Supplementary Appendix p. 10-11).

Discussion

In this national cohort study of 54,566 patients with PD, we found that 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. Increased frailty was associated with poorer health outcomes.

Our large-scale national data linkage cohort study adds to the limited evidence-base to evaluating the role of frailty in PD. One recent study found that frailty was associated with mortality in patients with PD (19), and similar findings have been reported in other respiratory

diseases(20). A recent systematic review showed that frail people had over a four-fold chance of dying from COPD (21) and another showed frail patients with interstitial lung disease were twice as likely to die (17). 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-specific mortality, length of first hospital stay and 90-day readmission to hospital. This study highlights the increased risk of mortality in frail patients with PD, and improving clinicians' understanding of this will enable them to devise patient-centred management strategies which prioritise symptomatic care in those who are unlikely to benefit from invasive management, or in those more severely frail with other comorbidities. Hence, these findings will have implication for the clinical management of this vulnerable group. Management is highly dependent on the underlying cause: investigation of the aetiology alone, with aspiration and thoracoscopic or surgical biopsies, is invasive and not without risk, with many patients requiring multiple aspirations or biopsies prior to obtaining a diagnosis or undergoing definitive management of their PD (22). Being frail may prohibit more invasive procedures, including surgical intervention. For many, there may be a significant long-term burden associated with their management, including repeated aspirations, further scans and outpatient appointments or treatment of an underlying malignancy, which may not be appropriate for frail patients with a limited 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 (23). In other words, they are unable to deal with the increased burden of developing a PD, which are commonly significant illnesses. Furthermore, the reduced physical activity and sarcopenia, which is associated with frailty (24), have been found to be an important prognostic factor in PD: sarcopenia has been found to be associated with poorer outcomes in patients with malignant PD-related to lung cancer (25, 26), and in patients with pleural effusion (27). Reduced physical activity has been implicated in pulmonary dysfunction and is linked to the development of sarcopenia (28). While 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 (28). Another potentially important biomarker which may provide mechanistic evidence for the association between frailty and poorer outcomes in patients with PD is chronic systemic inflammation. Frailty has been frequently and robustly associated with increased levels of C-reactive protein (CRP) (29), and inflammatory

responses in the pleura are responsible for the development of pleural effusion, and pleural scarring (30).

We also found that, within PD, frailty was associated with poorer hospital outcomes, including increased hospitalisation, increased hospital readmission, and longer time to hospital discharge. These findings, although not established within PD 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 readmission in patients with COPD (8), and following lung resection for cancer (31). Other authors have reported that 1 in 4 frail patients are readmitted within a month of index hospitalisation for a variety of causes (2).

This study used an eFI, which relies on General Practice data, it is a simple and easy to use accumulative deficit model. Assessing and reporting frailty in people with PD should be best clinical practice. This would allow clinicians and allied health care professionals to optimise patient care for patients with PD, 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 first hospital admission 0.4 years. Additionally like most diseases people in the lowest socio-economic groups were disproportionally affected (32). The impact of these findings will be to inform policy and guideline development for frail patients diagnosed with PD. These findings support clinical practice to reverse and slow increasing frailty with interventions such as exercise, nutrition, and the replacement of Vitamin D (28).

Strengths and limitations

This was a national cohort study following an *a priori* protocol published prior to accessing the data. The cohort included the majority of residents of Wales diagnosed with PD between 2005 and 2023. The Welsh population is broadly reflective of the wider UK population and those of Western Europe but may not reflect those of the wider European context. It is possible that frail individuals are more susceptible to PD due to factors such as decreased levels of physical activity, sarcopenia (24), chronic inflammation (29), or occupation (22, 29), data which were not accessible during this study. However, almost half of our cohort was classified as fit, suggesting that these cases of PD were not caused by frailty. It is worth noting that while the eFI has been shown to have good convergent validity (33) it also has a tendency to overestimate frailty when compared to other frailty measures (34). Additionally, the eFI has only been validated in populations aged 65 years and over (13), whereas our sample had a median age of 66 years, and thus a large number of people aged below 65. 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 PD. Whilst we focused on benign PD in this study, it is possible that a proportion of patients may have had, on further investigation, malignancy as the underlying cause. Removing cases of malignancy during follow-up, however, 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 (35). However, these are likely to be complex associations, and studies have been unable to distinguish the causes of such differences (e.g. migration and social deprivation).

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

Conclusions

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

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Declarations

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Contributions of authors

JH conceived the idea. JH, BC, NM, received funding for the project. AV carried out the systematic review of the literature. AV, BC, JH, NM developed the protocol, BC developed the statistical analysis plan, which was reviewed by EB, JH, NM. BC, RS analysed and interpreted the data. BC, RS authored the first draft of the manuscript. BC and RS had access to the source data. All authors reviewed and approved the manuscript. JH is the guarantor.

Data Sharing

This data was analysed within the SAIL secure data repository and is 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 (https://saildatabank.com).

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1: Sample characteristics by mortality status

		Alive (N=28,868) N (%)	Died (N=25,698) N (%)	Total N (%)
Frailty				
	Fit	18650 (69.1)	8344 (30.9)	26994 (49.5)
	Mild	7555 (45.5)	9038 (54.5)	16593 (30.4)
	Moderate	2189 (26.5)	6086 (73.5)	8275 (15.2)
	Severe	474 (17.5)	2230 (82.5)	2704 (5.0)
Age				
	Under 65	20972 (79.8)	5325 (20.2)	26297 (48.2)
	65-74	4330 (39.2)	6727 (60.8)	11057 (20.3)
	75-84	2786 (24.8)	8442 (75.2)	11228 (20.6)
	85 and over	780 (13.0)	5204 (87.0)	5984 (11.0)
Sex				
	Male	13647 (48.6)	14442 (51.4)	28089 (51.5)
	Female	15221 (57.5)	11256 (42.5)	26477 (48.5)
Smoking status				
	current	6097 (64.0)	3433 (36.0)	9530 (17.5)
	former	9986 (47.7)	10940 (52.3)	20926 (38.3)
	never	12785 (53.0)	11325 (47.0)	24110 (44.2)
WIMD				
	1	7074 (56.1)	5532 (43.9)	12606 (23.1)
	2	6245 (52.8)	5583 (47.2)	11828 (21.7)
	3	5979 (52.1)	5503 (47.9)	11482 (21.0)
	4	4888 (50.6)	4781 (49.4)	9669 (17.7)
	5	4671 (52.1)	4293 (47.9)	8964 (16.4)
	Missing			17 (0.0)
COPD				
	No	25433 (56.4)	19667 (43.6)	45100 (82.7)
	Yes	3435 (36.3)	6031 (63.7)	9466 (17.3)
Cardiac failure				
	No	27127 (57.3)	20246 (42.7)	47373 (86.8)
	Yes	1741 (24.2)	5452 (75.8)	7193 (13.2)
Diagnosis				
	J90/J91 Pleural effusion	21659 (50.8)	20975 (49.2)	42634 (78.1)
	J86 Pyothorax	1208 (59.5)	822 (40.5)	2030 (3.7)
	J92 Pleural plaque	978 (52.2)	895 (47.8)	1873 (3.4)
	J93 Pneumothorax	4825 (64.2)	2688 (35.8)	7513 (13.8)
	J94 Other pleural conditions	198 (38.4)	318 (61.6)	516 (0.9)
CCI				
	0	10324 (71.0)	4219 (29.0)	14543 (26.7)
	1	2009 (60.5)	1311 (39.5)	3320 (6.1)
	2	2659 (47.8)	2904 (52.2)	5563 (10.2)
	3	5885 (61.8)	3634 (38.2)	9519 (17.4)
	4	1980 (43.3)	2593 (56.7)	4573 (8.4)
	5+	6011 (35.3)	11037 (64.7)	17048 (31.2)

Note: COPD=chronic obstructive pulmonary disease; CCI= Charlson Comorbidity Index; WIMD=Welsh index of multiple deprivation

Table 2: Time to all-cause mortality (N=54,566; 25,698 events).

		HR (95% CI)	p	aHR (95% CI)	p
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					
	Under 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 and over	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	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

Note: CI=confidence interval; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; aHR=adjusted HR; WIMD=Welsh index of multiple deprivation

Table 3: Time to first hospital admission (any cause); N=54,566 (34,687 events)

		HR (95% CI)	p	aHR (95% CI)	p
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					
	Under 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 and over	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

Note: CI=confidence interval; CCI= Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; aHR=adjusted HR; WIMD=Welsh index of multiple deprivation

Figure 1: Flowchart showing cohort size for each analysis

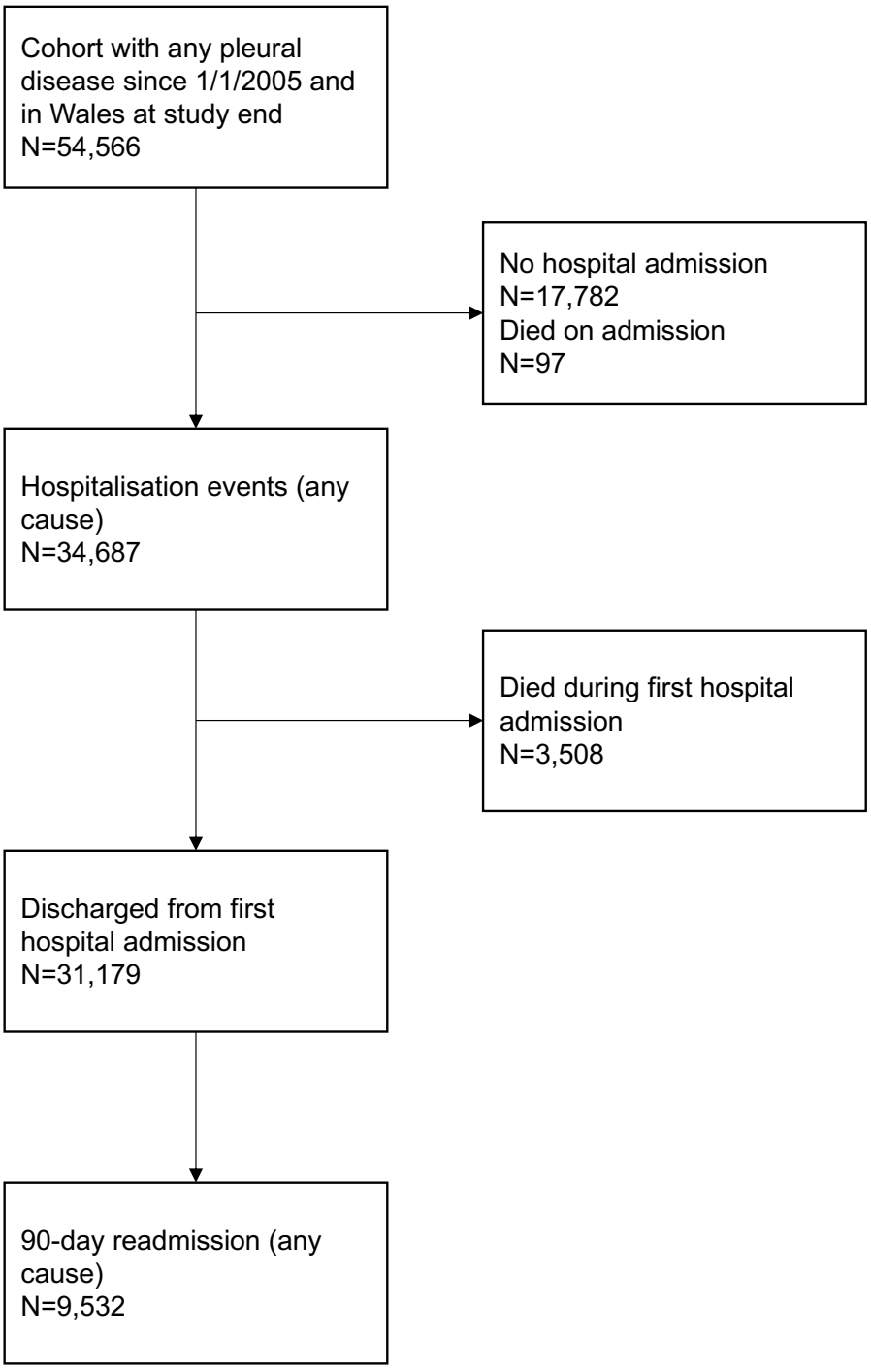


Figure 2: Kaplan-Meier survival plot showing overall survival by eFI frailty categories (N=54,566)

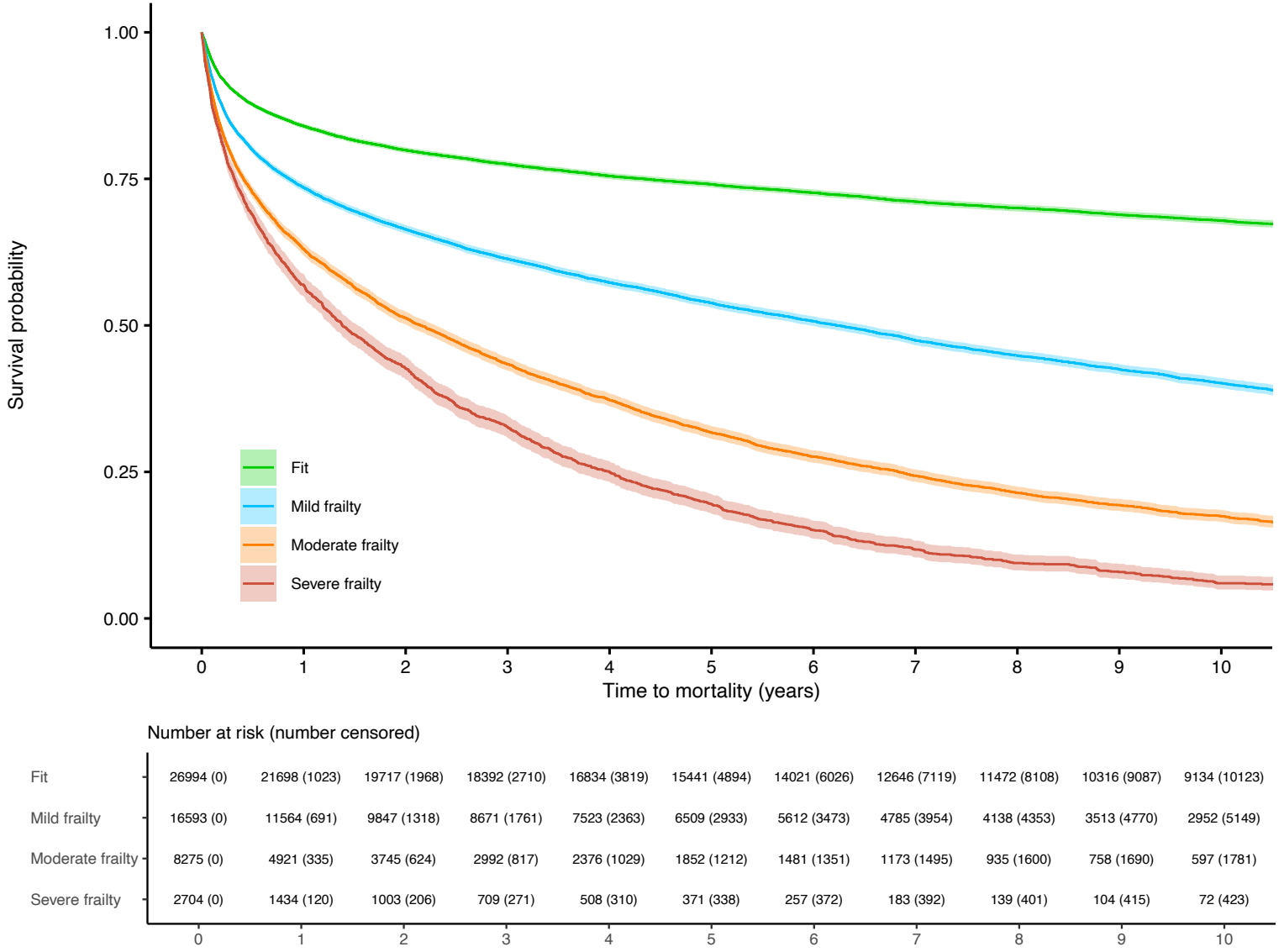


Table S1: Time to mortality due to pleural disease (N=54,566; 392 events)

		HR (95% CI)	p	aHR (95% CI)	p
Frailty					
	Fit	1 (ref)	-	1 (ref)	-
	Mild	1.97 (1.50-2.58)	<0.0001	1.12 (0.81-1.55)	0.51
	Moderate	4.11 (3.13-5.39)	<0.0001	1.49 (1.03-2.14)	0.032
	Severe	6.30 (4.48-8.86)	<0.0001	1.75 (1.12-2.72)	0.013
Age					
	Under 65	1 (ref)	-	1 (ref)	-
	65-74	3.54 (2.40-5.24)	<0.0001	2.89 (1.92-4.35)	<0.0001
	75-84	6.76 (4.72-9.67)	<0.0001	4.79 (3.24-7.08)	<0.0001
	85 and over	21.41 (15.13-30.31)	<0.0001	13.60 (9.20-20.13)	<0.0001
Sex					
	Male	1 (ref)	-	1 (ref)	-
	Female	0.91 (0.74-1.12)	0.36	0.74 (0.60-0.91)	0.0052
Smoking status					
	Current	0.37 (0.25-0.55)	<0.0001	0.89 (0.59-1.35)	0.59
	Former	0.81 (0.66-1.01)	0.059	0.86 (0.68-1.08)	0.20
	Never	1 (ref)	-	1 (ref)	-
WIMD					
	1	0.75 (0.53-1.07)	0.11	1.06 (0.75-1.51)	0.73
	2	0.89 (0.64-1.25)	0.51	1.06 (0.75-1.49)	0.73
	3	1.11 (0.80-1.54)	0.55	1.26 (0.90-1.75)	0.18
	4	1.04 (0.74-1.46)	0.83	1.10 (0.78-1.56)	0.57
	5	1 (ref)	-	1 (ref)	-
COPD					
	No	1 (ref)	-	1 (ref)	-
	Yes	0.85 (0.65-1.12)	0.25	0.79 (0.59-1.06)	0.12
Cardiac failure					
	No	1 (ref)	-	1 (ref)	-
	Yes	1.80 (1.41-2.29)	<0.0001	0.71 (0.55-0.92)	0.0087
Diagnosis					
	J90/J91 Pleural effusion	1 (ref)	-	1 (ref)	-
	J86 Pyothorax	0.16 (0.07-0.40)	<0.0001	0.29 (0.12-0.71)	0.0065
	J92 Pleural plaque	0.27 (0.10-0.73)	0.0096	0.21 (0.08-0.57)	0.0021
	J93 Pneumothorax	0.06 (0.03-0.13)	<0.0001	0.11 (0.05-0.24)	<0.0001
	J94 Other pleural	0.33 (0.10-1.02)	0.054	0.44 (0.14-1.39)	0.16
CCI					
	0	1 (ref)	-	1 (ref)	-
	1	0.81 (0.44-1.50)	0.51	0.53 (0.28-1.00)	0.052
	2	1.59 (1.08-2.34)	0.019	1.05 (0.70-1.59)	0.80
	3	0.71 (0.46-1.08)	0.11	0.65 (0.41-1.03)	0.068
	4	1.89 (1.28-2.80)	0.0014	1.01 (0.64-1.58)	0.97
	5+	2.55 (1.94-3.35)	<0.0001	1.12 (0.77-1.63)	0.54

Note: CI=confidence interval; CCI= Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; aHR=adjusted HR; WIMD=Welsh index of multiple deprivation

Table S2: Time to first hospitalisation for pleural disease; N=54,566 (4,785 events)

		HR (95% CI)	p	aHR (95% CI)	p
Frailty					
	Fit	1 (ref)	-	1 (ref)	-
	Mild	1.05 (0.98-1.12)	0.13	0.99 (0.91-1.07)	0.79
	Moderate	1.04 (0.96-1.13)	0.31	0.99 (0.89-1.10)	0.83
	Severe	0.89 (0.76-1.03)	0.11	0.88 (0.74-1.03)	0.12
Age					
	Under 65	1 (ref)	-	1 (ref)	-
	65-74	1.08 (1.01-1.17)	0.032	1.06 (0.98-1.14)	0.17
	75-84	1.10 (1.02-1.18)	0.013	1.07 (0.99-1.16)	0.11
	85 and over	0.90 (0.81-0.99)	0.035	0.90 (0.80-1.00)	0.059
Sex					
	Male	1 (ref)	-	1 (ref)	-
	Female	0.75 (0.71-0.80)	<0.0001	0.75 (0.70-0.79)	<0.0001
Smoking status					
	Current	1.01 (0.93-1.10)	0.78	0.99 (0.91-1.09)	0.90
	Former	1.17 (1.10-1.25)	<0.0001	1.12 (1.05-1.19)	0.0011
	Never	1 (ref)	-	1 (ref)	-
WIMD					
	1	0.92 (0.84-1.01)	0.078	0.94 (0.86-1.03)	0.19
	2	0.94 (0.85-1.03)	0.17	0.95 (0.86-1.04)	0.25
	3	0.96 (0.87-1.05)	0.39	0.97 (0.88-1.06)	0.48
	4	1.01 (0.92-1.12)	0.76	1.02 (0.93-1.13)	0.65
	5	1 (ref)	-	1 (ref)	-
COPD					
	No	1 (ref)	-	1 (ref)	-
	Yes	0.94 (0.87-1.01)	0.095	0.86 (0.80-0.93)	0.0002
Cardiac failure					
	No	1 (ref)	-	1 (ref)	-
	Yes	0.87 (0.80-0.95)	0.0010	0.83 (0.77-0.91)	<0.0001
Diagnosis					
	J90/J91 Pleural effusion	1 (ref)	-	1 (ref)	-
	J86 Pyothorax	0.63 (0.55-0.72)	<0.0001	0.60 (0.52-0.69)	<0.0001
	J92 Pleural plaque	0.86 (0.70-1.07)	0.18	0.77 (0.62-0.95)	0.017
	J93 Pneumothorax	1.02 (0.95-1.09)	0.65	0.97 (0.90-1.05)	0.50
	J94 Other pleural conditions	0.89 (0.73-1.09)	0.25	0.86 (0.71-1.05)	0.14
CCI					
	0	1 (ref)	-	1 (ref)	-
	1	1.03 (0.90-1.19)	0.65	1.03 (0.89-1.18)	0.71
	2	1.19 (1.07-1.31)	0.0008	1.18 (1.07-1.31)	0.0016
	3	1.22 (1.11-1.33)	<0.0001	1.23 (1.13-1.36)	<0.0001
	4	1.10 (0.98-1.23)	0.10	1.13 (1.00-1.28)	0.051
	5+	1.16 (1.08-1.25)	<0.0001	1.21 (1.10-1.34)	0.0001

Note: CI=confidence interval; CCI= Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; aHR=adjusted HR; WIMD=Welsh index of multiple deprivation

Table S3: Length of first admission (any cause); N=34,687 (31,179 events)

		HR (95% CI)	p	aHR (95% CI)	p
Frailty					
	Fit	1 (ref)	-	1 (ref)	-
	Mild	0.79 (0.77-0.81)	<0.0001	0.95 (0.92-0.98)	0.0011
	Moderate	0.64 (0.62-0.66)	<0.0001	0.90 (0.86-0.93)	<0.0001
	Severe	0.56 (0.53-0.59)	<0.0001	0.86 (0.81-0.91)	<0.0001
Age					
	Under 65	1 (ref)	-	1 (ref)	-
	65-74	0.69 (0.67-0.71)	<0.0001	0.72 (0.69-0.74)	<0.0001
	75-84	0.54 (0.53-0.56)	<0.0001	0.58 (0.56-0.60)	<0.0001
	85 and over	0.41 (0.40-0.43)	<0.0001	0.45 (0.43-0.47)	<0.0001
Sex					
	Male	1 (ref)	-	1 (ref)	-
	Female	1.06 (1.04-1.08)	<0.0001	1.05 (1.02-1.07)	<0.0001
Smoking status					
	Current	1.18 (1.14-1.22)	<0.0001	0.99 (0.96-1.03)	0.59
	Former	1.00 (0.98-1.03)	0.72	1.02 (0.99-1.05)	0.13
	Never	1 (ref)	-	1 (ref)	-
WIMD					
	1	1.06 (1.02-1.10)	0.0044	0.98 (0.95-1.02)	0.43
	2	1.02 (0.98-1.06)	0.39	0.98 (0.94-1.02)	0.33
	3	0.98 (0.95-1.02)	0.43	0.97 (0.93-1.01)	0.11
	4	0.97 (0.93-1.01)	0.12	0.97 (0.93-1.00)	0.084
	5	1 (ref)	-	1 (ref)	-
COPD					
	No	1 (ref)	-	1 (ref)	-
	Yes	0.94 (0.91-0.96)	<0.0001	1.01 (0.98-1.04)	0.70
Cardiac failure					
	No	1 (ref)	-	1 (ref)	-
	Yes	0.73 (0.71-0.76)	<0.0001	0.91 (0.88-0.94)	<0.0001
Diagnosis					
	J90/J91 Pleural effusion	1 (ref)	-	1 (ref)	-
	J86 Pyothorax	0.99 (0.93-1.05)	0.77	0.82 (0.77-0.87)	<0.0001
	J92 Pleural plaque	0.97 (0.92-1.03)	0.39	1.06 (1.00-1.13)	0.050
	J93 Pneumothorax	1.13 (1.09-1.17)	<0.0001	0.97 (0.93-1.00)	0.045
	J94 Other pleural conditions	0.97 (0.87-1.09)	0.62	0.87 (0.78-0.97)	0.015
CCI					
	0	1 (ref)	-	1 (ref)	-
	1	0.82 (0.78-0.87)	<0.0001	0.91 (0.87-0.96)	0.0006
	2	0.82 (0.79-0.86)	<0.0001	0.90 (0.86-0.94)	<0.0001
	3	0.92 (0.88-0.95)	<0.0001	0.97 (0.94-1.01)	0.12
	4	0.74 (0.71-0.77)	<0.0001	0.88 (0.84-0.92)	<0.0001
	5+	0.69 (0.67-0.71)	<0.0001	0.91 (0.88-0.95)	<0.0001

Note: CI=confidence interval; CCI= Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; aHR=adjusted HR; WIMD=Welsh index of multiple deprivation

Table S4: Length of stay of first hospital admission due to pleural disease; N=4,787 (4,403 events)

		HR (95% CI)	p	aHR (95% CI)	p
Frailty					
	Fit	1 (ref)	-	1 (ref)	-
	Mild	0.85 (0.80-0.91)	<0.0001	0.95 (0.87-1.03)	0.18
	Moderate	0.75 (0.69-0.82)	<0.0001	0.91 (0.81-1.02)	0.093
	Severe	0.64 (0.55-0.75)	<0.0001	0.85 (0.71-1.02)	0.074
Age					
	Under 65	1 (ref)	-	1 (ref)	-
	65-74	0.86 (0.80-0.93)	<0.0001	0.88 (0.81-0.95)	0.0016
	75-84	0.74 (0.69-0.80)	<0.0001	0.74 (0.68-0.81)	<0.0001
	85 and over	0.54 (0.49-0.61)	<0.0001	0.56 (0.49-0.63)	<0.0001
Sex					
	Male	1 (ref)	-	1 (ref)	-
	Female	0.91 (0.85-0.97)	0.0022	0.90 (0.84-0.96)	0.0013
Smoking status					
	Current	1.10 (1.00-1.20)	0.044	1.03 (0.93-1.13)	0.60
	Former	1.04 (0.98-1.11)	0.20	1.06 (0.99-1.14)	0.10
	Never	1 (ref)	-	1 (ref)	-
WIMD					
	1	0.96 (0.88-1.06)	0.44	0.94 (0.85-1.04)	0.21
	2	0.88 (0.80-0.97)	0.011	0.87 (0.79-0.96)	0.0052
	3	0.96 (0.87-1.06)	0.43	0.95 (0.86-1.05)	0.31
	4	0.93 (0.84-1.03)	0.14	0.94 (0.85-1.03)	0.20
	5	1 (ref)	-	1 (ref)	-
COPD					
	No	1 (ref)	-	1 (ref)	-
	Yes	0.93 (0.86-1.00)	0.063	0.93 (0.86-1.01)	0.11
Cardiac failure					
	No	1 (ref)	-	1 (ref)	-
	Yes	0.83 (0.76-0.90)	<0.0001	0.95 (0.87-1.04)	0.26
Diagnosis					
	J90/J91 Pleural effusion	1 (ref)	-	1 (ref)	-
	J86 Pyothorax	0.79 (0.68-0.90)	0.0007	0.66 (0.58-0.77)	<0.001
	J92 Pleural plaque	1.65 (1.32-2.07)	<0.0001	1.58 (1.26-1.99)	<0.001
	J93 Pneumothorax	1.13 (1.05-1.21)	0.0008	0.94 (0.87-1.02)	0.16
	J94 Other pleural conditions	0.89 (0.72-1.09)	0.25	0.77 (0.62-0.94)	0.011
CCI					
	0	1 (ref)	-	1 (ref)	-
	1	0.97 (0.84-1.11)	0.64	1.01 (0.87-1.17)	0.90
	2	0.95 (0.86-1.06)	0.37	0.99 (0.89-1.10)	0.82
	3	0.98 (0.90-1.08)	0.74	1.03 (0.94-1.13)	0.55
	4	0.81 (0.72-0.92)	0.0007	0.91 (0.80-1.03)	0.14
	5+	0.81 (0.75-0.88)	<0.0001	0.95 (0.86-1.05)	0.36

Note: CI=confidence interval; CCI= Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; aHR=adjusted HR; WIMD=Welsh index of multiple deprivation

Table S5: Logistic regression analysing readmission within 90 days of any-cause hospitalisation (N=31,179)

		HR (95% CI)	p	aHR (95% CI)	p
Frailty					
	Fit	1 (ref)	-	1 (ref)	-
	Mild	1.26 (1.19-1.33)	<0.0001	1.06 (0.99-1.13)	0.086
	Moderate	1.59 (1.48-1.70)	<0.0001	1.20 (1.10-1.31)	<0.0001
	Severe	1.79 (1.60-1.99)	<0.0001	1.27 (1.11-1.44)	0.0003
Age					
	Under 65	1 (ref)	-	1 (ref)	-
	65-74	1.35 (1.27-1.44)	<0.0001	1.19 (1.12-1.28)	<0.0001
	75-84	1.54 (1.44-1.64)	<0.0001	1.27 (1.18-1.37)	<0.0001
	85 and over	1.52 (1.39-1.66)	<0.0001	1.19 (1.08-1.31)	0.0006
Sex					
	Male	1 (ref)	-	1 (ref)	-
	Female	0.91 (0.87-0.96)	0.0003	0.91 (0.87-0.96)	0.0007
Smoking status					
	Current	0.91 (0.85-0.98)	0.013	1.01 (0.93-1.09)	0.81
	Former	1.07 (1.01-1.13)	0.015	1.01 (0.96-1.07)	0.66
	Never	1 (ref)	-	1 (ref)	-
WIMD					
	1	0.91 (0.83-0.98)	0.018	0.94 (0.87-1.03)	0.17
	2	0.97 (0.90-1.06)	0.52	0.99 (0.91-1.08)	0.82
	3	0.92 (0.85-1.00)	0.051	0.93 (0.85-1.01)	0.077
	4	0.98 (0.90-1.07)	0.60	0.98 (0.90-1.07)	0.65
	5	1 (ref)	-	1 (ref)	-
COPD					
	No	1 (ref)	-	1 (ref)	-
	Yes	1.10 (1.04-1.17)	0.0014	0.99 (0.93-1.06)	0.79
Cardiac failure					
	No	1 (ref)	-	1 (ref)	-
	Yes	1.45 (1.36-1.54)	<0.0001	1.18 (1.10-1.26)	0.0004
Diagnosis					
	J90/J91 Pleural effusion	1 (ref)	-	1 (ref)	-
	J86 Pyothorax	0.74 (0.65-0.85)	<0.0001	0.82 (0.72-0.94)	0.0045
	J92 Pleural plaque	0.83 (0.72-0.95)	0.0065	0.73 (0.64-0.84)	<0.0001
	J93 Pneumothorax	0.77 (0.72-0.83)	<0.0001	0.87 (0.80-0.94)	0.0004
	J94 Other pleural conditions	0.73 (0.57-0.93)	0.0098	0.77 (0.60-0.98)	0.034
CCI					
	0	1 (ref)	-	1 (ref)	-
	1	1.11 (0.99-1.25)	0.067	1.02 (0.91-1.15)	0.75
	2	1.46 (1.33-1.60)	<0.0001	1.34 (1.22-1.47)	<0.0001
	3	1.14 (1.05-1.23)	0.0016	1.10 (1.01-1.19)	0.035
	4	1.48 (1.34-1.63)	<0.0001	1.28 (1.15-1.42)	<0.0001
	5+	1.58 (1.48-1.69)	<0.0001	1.27 (1.16-1.38)	<0.0001

Note: CI=confidence interval; CCI= Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; aHR=adjusted HR; WIMD=Welsh index of multiple deprivation

Table S6 Logistic regression analysing 90-day readmission from initial admission due to pleural disease (N=4,403)

		HR (95% CI)	p	aHR (95% CI)	p
Frailty					
	Fit	1 (ref)	-	1 (ref)	-
	Mild	1.25 (1.09-1.44)	0.0012	1.13 (0.96-1.34)	0.14
	Moderate	1.34 (1.13-1.60)	0.0010	1.16 (0.92-1.45)	0.20
	Severe	1.41 (1.03-1.92)	0.033	1.18 (0.83-1.69)	0.36
Age					
	Under 65	1 (ref)	-	1 (ref)	-
	65-74	1.33 (1.14-1.55)	0.00021	1.11 (0.94-1.31)	0.24
	75-84	1.31 (1.12-1.53)	0.0006	1.02 (0.86-1.22)	0.78
	85 and over	1.24 (1.00-1.54)	0.053	0.91 (0.72-1.17)	0.47
Sex					
	Male	1 (ref)	-	1 (ref)	-
	Female	1.21 (1.07-1.38)	0.0026	1.17 (1.03-1.33)	0.019
Smoking status					
	Current	0.79 (0.66-0.95)	0.013	0.93 (0.76-1.13)	0.44
	Former	0.96 (0.85-1.10)	0.58	1.01 (0.88-1.16)	0.86
	Never	1 (ref)	-	1 (ref)	-
WIMD					
	1	0.79 (0.65-0.96)	0.017	0.84 (0.69-1.02)	0.077
	2	0.92 (0.76-1.12)	0.43	0.97 (0.80-1.19)	0.80
	3	0.77 (0.63-0.94)	0.0091	0.79 (0.65-0.96)	0.018
	4	0.88 (0.72-1.07)	0.21	0.91 (0.74-1.11)	0.35
	5	1 (ref)	-	1 (ref)	-
COPD					
	No	1 (ref)	-	1 (ref)	-
	Yes	0.92 (0.79-1.08)	0.32	0.95 (0.80-1.13)	0.56
Cardiac failure					
	No	1 (ref)	-	1 (ref)	-
	Yes	1.23 (1.04-1.46)	0.018	1.05 (0.87-1.26)	0.61
Diagnosis					
	J90/J91 Pleural effusion	1 (ref)	-	1 (ref)	-
	J86 Pyothorax	0.59 (0.44-0.78)	0.0003	0.64 (0.47-0.86)	0.0033
	J92 Pleural plaque	0.85 (0.54-1.33)	0.47	0.92 (0.58-1.45)	0.71
	J93 Pneumothorax	0.60 (0.52-0.69)	<0.0001	0.67 (0.57-0.79)	<0.0001
	J94 Other pleural conditions	0.72 (0.48-1.10)	0.13	0.77 (0.50-1.17)	0.22
CCI					
	0	1 (ref)	-	1 (ref)	-
	1	0.96 (0.72-1.29)	0.80	0.83 (0.62-1.12)	0.23
	2	1.26 (1.02-1.56)	0.029	1.05 (0.84-1.31)	0.66
	3	0.86 (0.71-1.03)	0.11	0.84 (0.69-1.02)	0.079
	4	1.20 (0.94-1.53)	0.14	1.01 (0.77-1.31)	0.96
	5+	1.20 (1.02-1.40)	0.027	0.98 (0.80-1.21)	0.88

Note: CI=confidence interval; CCI= Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; aHR=adjusted HR; WIMD=Welsh index of multiple deprivation

Figure S 1: Kaplan-Meier showing time to first any-cause hospitalisation (N=54,566)

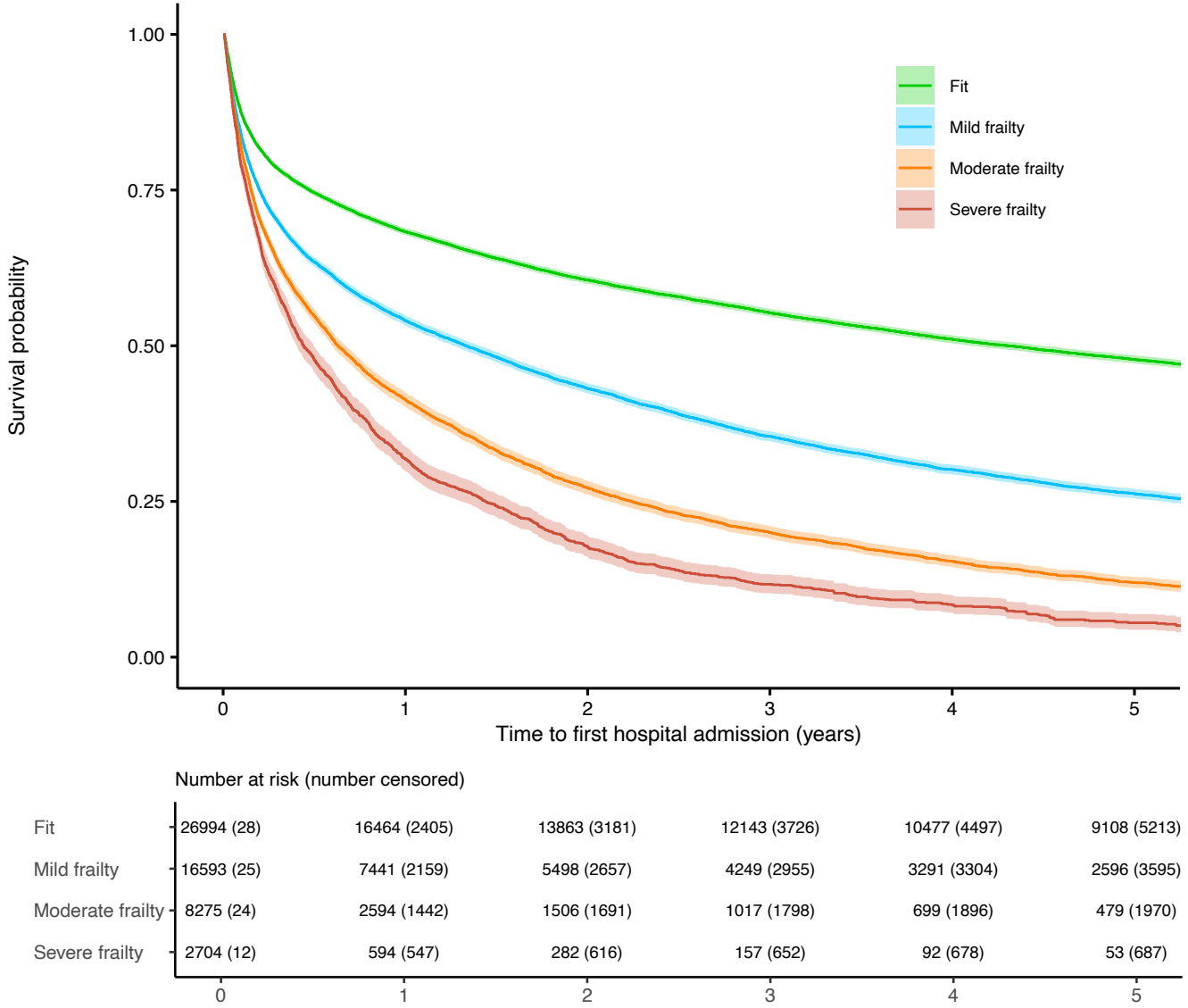


Figure S 2: Kaplan-Meier plot showing length of stay of first any-cause hospitalisation (N=34,687)

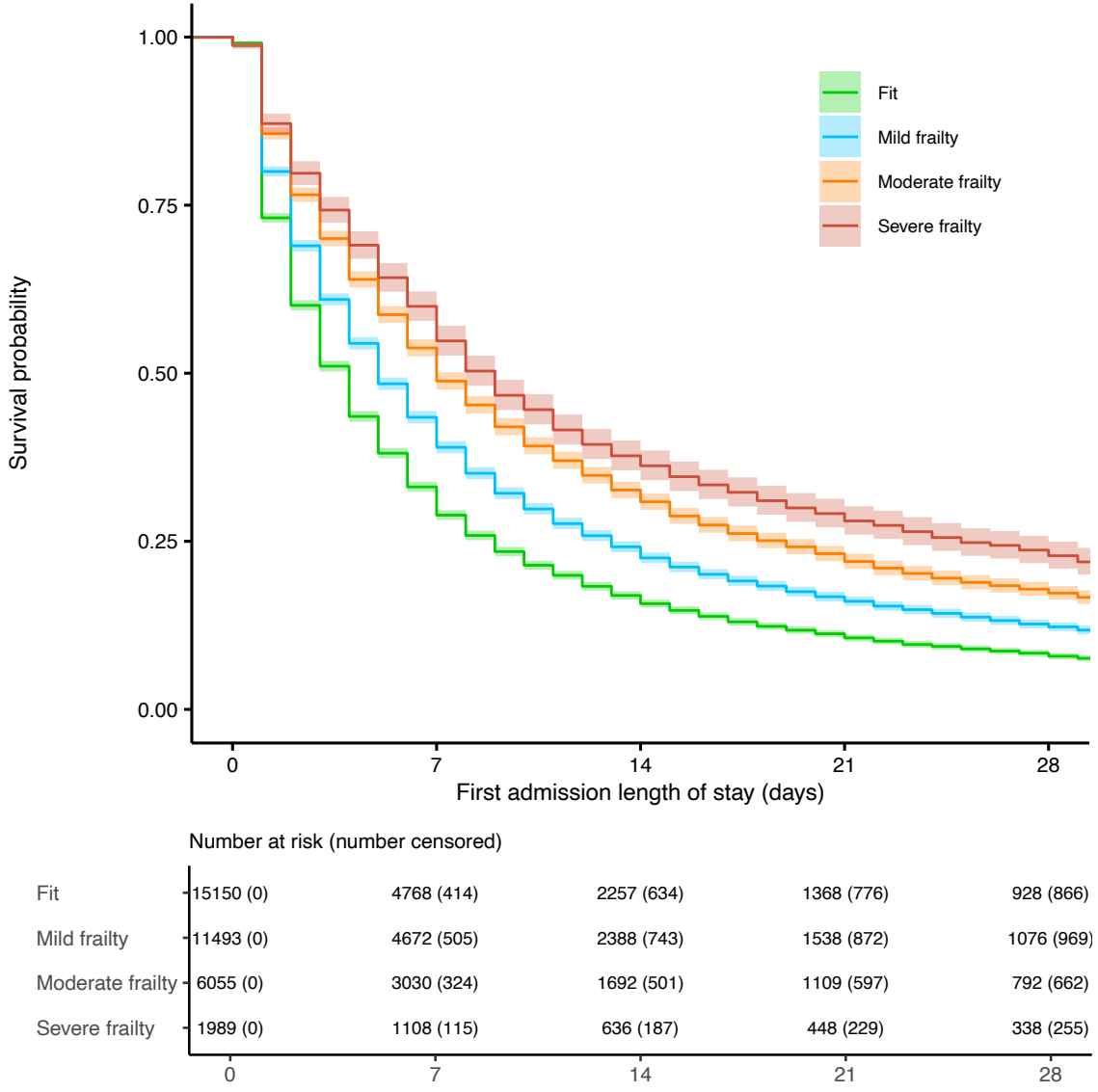
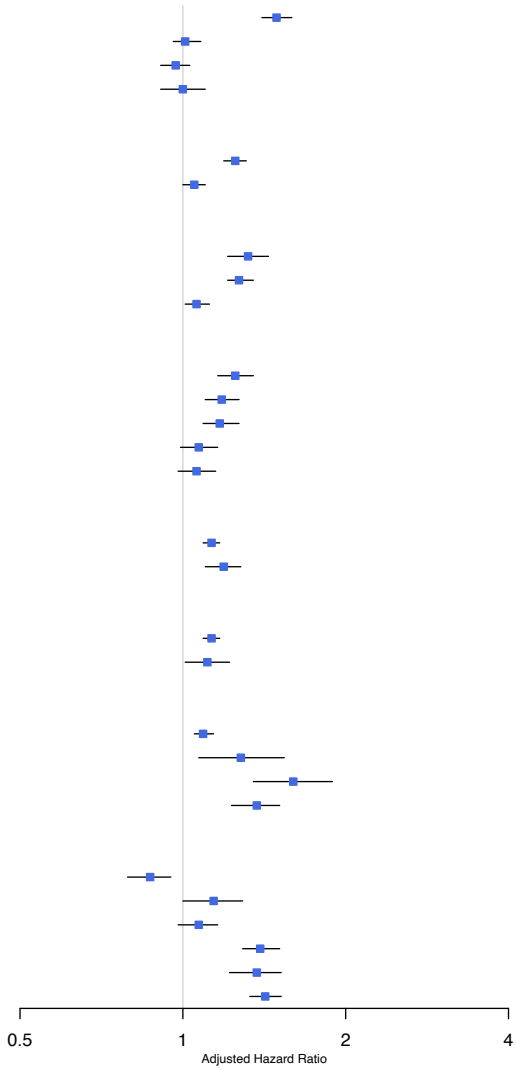


Figure S 3: Subgroup analyses for time to all cause mortality (presenting adjusted[&] Hazard Ratios and 95% confidence intervals [CI]) comparing fit vs frail (mild, moderate or severe frailty) patients (N=54,566)

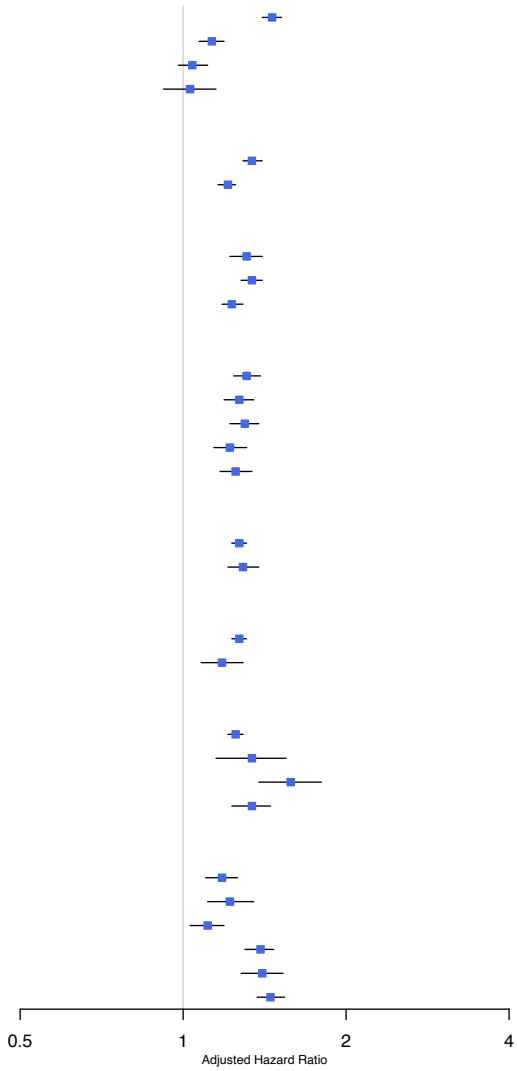
Subgroup	Frail n/N	Adjusted Hazard Ratio (95% CI)	P
Age			
Under 65	7335/26297	1.49 (1.40–1.59)	<0.0001
65–74	6737/11057	1.01 (0.96–1.08)	0.64
75–84	8502/11228	0.97 (0.91–1.03)	0.31
85 and over	4998/5984	1.00 (0.91–1.10)	0.93
Sex			
Male	13696/28089	1.25 (1.19–1.31)	<0.0001
Female	13876/26477	1.05 (1.00–1.10)	0.072
Smoking status			
Current	3805/9530	1.32 (1.21–1.44)	<0.0001
Former	12593/20926	1.27 (1.21–1.35)	<0.0001
Never	11174/24110	1.06 (1.01–1.12)	0.026
WIMD Quintile			
1st	6262/12606	1.25 (1.16–1.35)	<0.0001
2nd	6051/11828	1.18 (1.10–1.27)	<0.0001
3rd	5963/11482	1.17 (1.09–1.27)	<0.0001
4th	4873/9669	1.07 (0.99–1.16)	0.094
5th	4418/8964	1.06 (0.98–1.15)	0.16
COPD			
No	20729/45100	1.13 (1.09–1.17)	<0.0001
Yes	6843/9466	1.19 (1.10–1.28)	<0.0001
Heart Failure			
No	21570/47373	1.13 (1.09–1.17)	<0.0001
Yes	6002/7193	1.11 (1.01–1.22)	0.025
Index diagnosis			
Pleural effusion (J90/J91)	22951/42634	1.09 (1.05–1.14)	<0.0001
Pyothorax (J86)	746/2030	1.28 (1.07–1.54)	0.008
Pleural plaque (J92)	1098/1873	1.60 (1.35–1.89)	<0.0001
Pneumothorax (J93)	2537/7513	1.37 (1.23–1.51)	<0.0001
CCI			
0	1719/14543	0.87 (0.79–0.95)	0.0027
1	1566/3320	1.14 (1.00–1.29)	0.047
2	2468/5563	1.07 (0.98–1.16)	0.11
3	4080/9519	1.39 (1.29–1.51)	<0.0001
4	3344/4573	1.37 (1.22–1.52)	<0.0001
5+	14395/17048	1.42 (1.33–1.52)	<0.0001



[&]Analyses adjusted for age, sex, smoking status, Welsh index of multiple (WIMD) deprivation quintile, chronic obstructive pulmonary disease (COPD), heart failure, and index pleural disease diagnosis, and Charlson comorbidity index (CCI).

Figure S 4: Subgroup analyses for time to any cause hospitalisation (presenting adjusted[&] Hazard Ratios and 95% confidence intervals [CI]) comparing fit vs frail (mild, moderate or severe frailty) patients (N=54,566)

Subgroup	Frail n/N	Adjusted Hazard Ratio (95% CI)	P
Age			
Under 65	7335/26297	1.46 (1.40–1.52)	<0.0001
65–74	6737/11057	1.13 (1.07–1.19)	<0.0001
75–84	8502/11228	1.04 (0.98–1.11)	0.17
85 and over	4998/5984	1.03 (0.92–1.15)	0.58
Sex			
Male	13696/28089	1.34 (1.29–1.40)	<0.0001
Female	13876/26477	1.21 (1.16–1.25)	<0.0001
Smoking status			
Current	3805/9530	1.31 (1.22–1.40)	<0.0001
Former	12593/20926	1.34 (1.28–1.40)	<0.0001
Never	11174/24110	1.23 (1.18–1.29)	<0.0001
WIMD Quintile			
1st	6262/12606	1.31 (1.24–1.39)	<0.0001
2nd	6051/11828	1.27 (1.19–1.35)	<0.0001
3rd	5963/11482	1.30 (1.22–1.38)	<0.0001
4th	4873/9669	1.22 (1.14–1.31)	<0.0001
5th	4418/8964	1.25 (1.17–1.34)	<0.0001
COPD			
No	20729/45100	1.27 (1.23–1.31)	<0.0001
Yes	6843/9466	1.29 (1.21–1.38)	<0.0001
Heart Failure			
No	21570/47373	1.27 (1.23–1.31)	<0.0001
Yes	6002/7193	1.18 (1.08–1.29)	0.0003
Index diagnosis			
Pleural effusion (J90/J91)	22951/42634	1.25 (1.21–1.29)	<0.0001
Pyothorax (J86)	746/2030	1.34 (1.15–1.55)	0.0001
Pleural plaque (J92)	1098/1873	1.58 (1.38–1.80)	<0.0001
Pneumothorax (J93)	2537/7513	1.34 (1.23–1.45)	<0.0001
CCI			
0	1719/14543	1.18 (1.10–1.26)	<0.0001
1	1566/3320	1.22 (1.11–1.35)	0.0001
2	2468/5563	1.11 (1.03–1.19)	0.0078
3	4080/9519	1.39 (1.30–1.47)	<0.0001
4	3344/4573	1.40 (1.28–1.53)	<0.0001
5+	14395/17048	1.45 (1.37–1.54)	<0.0001



[&]Analyses adjusted for age, sex, smoking status, Welsh index of multiple deprivation (WIMD) quintile, chronic obstructive pulmonary disease (COPD), heart failure, index pleural disease diagnosis, and Charlson comorbidity index (CCI).