

# **Clinical frailty adds to acute illness severity in predicting mortality in hospitalized older adults: an observational study**

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Short running title: Frailty, acuity and inpatient mortality

Authors' contributions: Roman Romero-Ortuno conceived the study, collected and interpreted data, performed statistical analyses, and prepared the manuscript. Stephen Wallis and Richard Biram collected and interpreted data and revised the manuscript critically for important intellectual content. Victoria Keevil performed statistical analyses, interpreted data, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript before submission.

**Abstract**

**Aim:** frail individuals may be at higher risk of death from a given acute illness severity (AIS), but this relationship has not been studied in an English National Health Service (NHS) acute hospital setting.

**Methods:** this was a retrospective observational study in a large university NHS hospital in England. We analyzed all first non-elective inpatient episodes of people aged  $\geq 75$  years (all specialties) between October 2014 and October 2015. Pre-admission frailty was assessed with the Clinical Frailty Scale (CFS) of the Canadian Study on Health & Aging, and AIS in the Emergency Department was measured with a Modified Early Warning Score (ED-MEWS $<4$  was considered as low acuity, and ED-MEWS $\geq 4$  as high acuity). A survival analysis compared times to 30-day inpatient death between CFS categories (1-4: very fit to vulnerable, 5: mildly frail, 6: moderately frail, and 7-8: severely or very severely frail).

**Results:** there were 12282 non-elective patient episodes (8202 first episodes, of which complete data was available for 5505). In a Cox proportional hazards model controlling for age, gender, Charlson Comorbidity Index, history of dementia, current cognitive concern, and discharging specialty (medical versus surgical), ED-MEWS $\geq 4$  (HR=2.87, 95% CI: 2.27-3.62,  $p<0.001$ ), and CFS 7-8 (compared to CFS 1-4, HR=2.10, 95% CI: 1.52-2.92,  $p<0.001$ ) were independent predictors of survival time.

**Conclusions:** we found frailty and AIS independently associated with inpatient mortality after adjustment for confounders. Hospitals may find it informative to undertake large scale assessment of frailty (vulnerability), as well as AIS (stressor), in older patients admitted to hospital as emergencies.

**Key words**

Frail Elderly

Hospital Medicine

Mortality

Patient Acuity

Survival Analysis

## Introduction

Over the last decade widespread efforts within the English National Health Service (NHS) have been made to improve the early detection of patients at risk of adverse outcomes. In acute healthcare settings, such as Emergency Departments (EDs), patients have acute illness severity (AIS) information collected on arrival. One way of measuring AIS is by considering the degree of derangement of routinely collected physiological parameters, incorporated into an early warning score (EWS) [1]. Early warning scores grade the risk of patient deterioration and can help guide healthcare staff to escalate clinical care according to pre-specified protocols [2,3]. However, it has been suggested that AIS may not be the only driver of poor hospital outcomes, especially in those with a high burden of chronic disabling disease [4], and the proportion of older people admitted to NHS acute hospitals across England with pre-existing syndromes of multi-morbidity, cognitive impairment, mobility problems and physical dependency has increased dramatically over recent years [5].

Those syndromes can be identified early during the admission and may confer vulnerability to adverse outcomes due to reduced physiological reserve and ability to withstand acute stressors, a concept encapsulated by frailty. Frailty in older adults has been defined as a state of vulnerability due to cumulative decline in many physiological systems, which depletes homeostatic reserves and results in poor restoration of homeostasis after a stressor event triggering disproportionate changes in health status [6]. It is thought that physiological vulnerability in older adults is gradable along a continuum between fitness (or resilience) and frailty, and chronological age alone cannot accurately tell where a person is along that spectrum [7]. Indeed, the relationship

between chronological age and health status is very variable [8]. However, unlike AIS, frailty is not routinely measured in acute healthcare settings.

While the concept of frailty as an age-independent, gradable state of vulnerability to poor outcomes from stressors is quite uncontroversial [6], a number of approaches exist to its operationalization in clinical practice [9]. It is increasingly recognized that a gold standard approach for measuring frailty is neither appropriate nor desirable, and that different validated instruments can be suited to different settings and/or purposes [10,11]. In the NHS, the assessment of frailty in the acute, inpatient setting could add value to the management of the growing –but heterogeneous– population of older people [12-14]. Therefore, the measurement of frailty in acute settings is being encouraged by national initiatives such as the Acute Frailty Network (<http://www.acutefrailtynetwork.org.uk>). However, practitioners still report several major barriers preventing frailty from being rapidly measured at the front door [15], and there are still no national incentives to remove some of those barriers.

We utilized routinely collected data from a large tertiary university hospital in England where both AIS (proxy for acute stressor) and frailty (proxy for baseline vulnerability) are routinely measured on admission. We hypothesized that these two different entities may independently impact upon the risk of death in acute older adults. Previous research studies with frailty scores in acute settings have not been able to simultaneously consider AIS [16], and our aim was to study the relation between frailty, acuity and mortality in a real-world NHS setting.

## Methods

*Setting.* This retrospective observational study was conducted in a large tertiary university hospital in England with 1000 acute beds receiving over 102000 visits to the ED and admitting over 73000 patients per year; among the latter, over 12000 are aged 75 or more years.

*Sample.* We analyzed all first non-elective inpatient episodes (i.e. from ED admission to discharge) of people aged  $\geq 75$  years (all specialties) between the 26<sup>th</sup> of October 2014 and the 26<sup>th</sup> of October 2015. Data was obtained via the hospital's information systems following the implementation of a new electronic patient record (eHospital system) on the 26<sup>th</sup> of October 2014.

### *Patients' characteristics and outcomes*

The following variables were extracted from the hospital's information systems:

- Age and gender.
- Discharge specialty (medical versus surgical).
- Charlson Comorbidity Index (CCI, without age adjustment) [17]. The CCI is based on the discharge diagnoses, as coded by the 10<sup>th</sup> version of the WHO International Classification of Diseases (ICD-10). Therefore, it was calculated retrospectively and would have not been available to clinicians early during the patients' admission.
- Frailty. A frailty instrument that evaluates pre-admission comorbidity, cognitive impairment and disability is the Clinical Frailty Scale (CFS) of the Canadian Study on Health & Aging ([http://geriatricresearch.medicine.dal.ca/clinical\\_frailty\\_scale.htm](http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm)) [18]. The use of

the CFS has been found to be feasible in real-world acute NHS settings [19]. The use of the CFS in admissions of people aged  $\geq 75$  years was introduced in our center in 2013 under a local Commissioning for Quality and Innovation (CQUIN) scheme ([http://www.institute.nhs.uk/commissioning/pct\\_portal/cquin.html](http://www.institute.nhs.uk/commissioning/pct_portal/cquin.html)) [20]. The CQUIN required that all patients aged 75 years or over admitted to the hospital, via the emergency pathway, be screened for frailty using the CFS within 72 hours of admission. The new electronic patient admission screen includes a CFS scoring section as per [http://geriatricresearch.medicine.dal.ca/clinical\\_frailty\\_scale.htm](http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm). The admitting doctor usually scores the CFS, but it can also be completed by ED nurses or by nursing or therapy staff from the trust-wide Specialist Advice for the Frail Elderly (SAFE) team. Training on CFS scoring is provided to staff on induction and at regular educational meetings. In order to avoid confounding, patients with a CFS of 9 ('terminally ill' without being evidently frail) were excluded from the analyses. To avoid statistical underpower (due to a relatively low number of deaths), the original CFS categories were collapsed into four ordinal categories: up to vulnerable (CFS 1 to 4), mildly frail (CFS 5), moderately frail (CFS 6), and severely or very severely frail (CFS 7 or 8).

- AIS information is routinely collected by the nurses in the ED immediately after presentation (i.e. during the patient's triage) and throughout the patient's time in the ED (less than 4 hours in the majority of cases) using a Modified Early Warning Score (ED-MEWS). The components and scoring of the ED-MEWS are shown in Appendix A. Where more than one ED-MEWS was collected during the patient's time in the ED, the highest was used in the analyses. In our ED, the usual ED-

MEWS trigger for escalation (i.e. request for immediate medical review) is 4 or more points. Thus, ED-MEWS $\geq$ 4 defined high acuity in our analyses.

- Known history of dementia without a current cognitive concern (identified as ‘yes’ in the database). This was also collected by the admitting team within the first 72 hours of the admission in patients aged 75 or more, thanks to a parallel local CQUIN scheme. An additional variable was collected reflecting current cognitive concern without history of dementia (yes versus no).
- Length of stay (LOS, days).
- Inpatient mortality up to 30 days since admission (%). The rationale for the 30-day cut-off was to avoid capturing the deaths of long-stay patients, which could be less related to initial AIS. Information on detailed causes of death was not available on the service evaluation database.

*Statistical analyses.* All statistics were computed with IBM<sup>®</sup> SPSS<sup>®</sup> Statistics Version 22. The bivariate correlation between the ED-MEWS (continuous score) and the CFS categories was assessed with the two-sided Spearman’s *rho* correlation coefficient. Other bivariate comparisons were conducted with the non-parametric independent-samples Mann-Whitney U test (continuous versus dichotomous variables) or the Chi-squared test (between categorical variables), as appropriate. Ninety-five percent confidence intervals (CI) for 30-day inpatient mortality were computed.

Age and sex adjusted survival curves were calculated on the overall sample to compare times to 30-day inpatient death across CFS categories. A Cox proportional hazards regression model was used to test the independent effects of frailty and acuity in

predicting time to death while adjusting for age, gender, discharging specialty (medical vs. surgical), CCI, history of dementia, and current cognitive concern. Hazard Ratios (HR) with 95% CI were calculated for the predictors. To check the classification ability of the model, we saved the individual-level cumulative hazard function and we plotted it against 30-day inpatient mortality in an area under the curve (AUC) analysis. To check the proportional hazards (PH) assumption for the covariates, we plotted the cumulative hazards functions for the covariates, categorizing the continuous ones. Covariates were considered to fulfil the PH assumption if lines did not cross each other on the plots.

As a sensitivity analysis, the Cox proportional hazards regression analysis was repeated after imputing missing CFS and ED-MEWS scores using multiple imputation by chained equations.

*Ethics approval.* This Service Evaluation Audit was registered with our center's Safety and Quality Support Department (Project register number 3962). Formal confirmation was received that approval from the Ethics Committee was not required.

*Declaration of sources of funding.* This service evaluation did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Results

The initial database contained 12282 non-elective admission and discharge episodes of patients aged 75 or more years between the 26<sup>th</sup> of October 2014 and the 26<sup>th</sup> of October 2015 (all specialties). Among those, 8202 (66.8%) were first episodes.

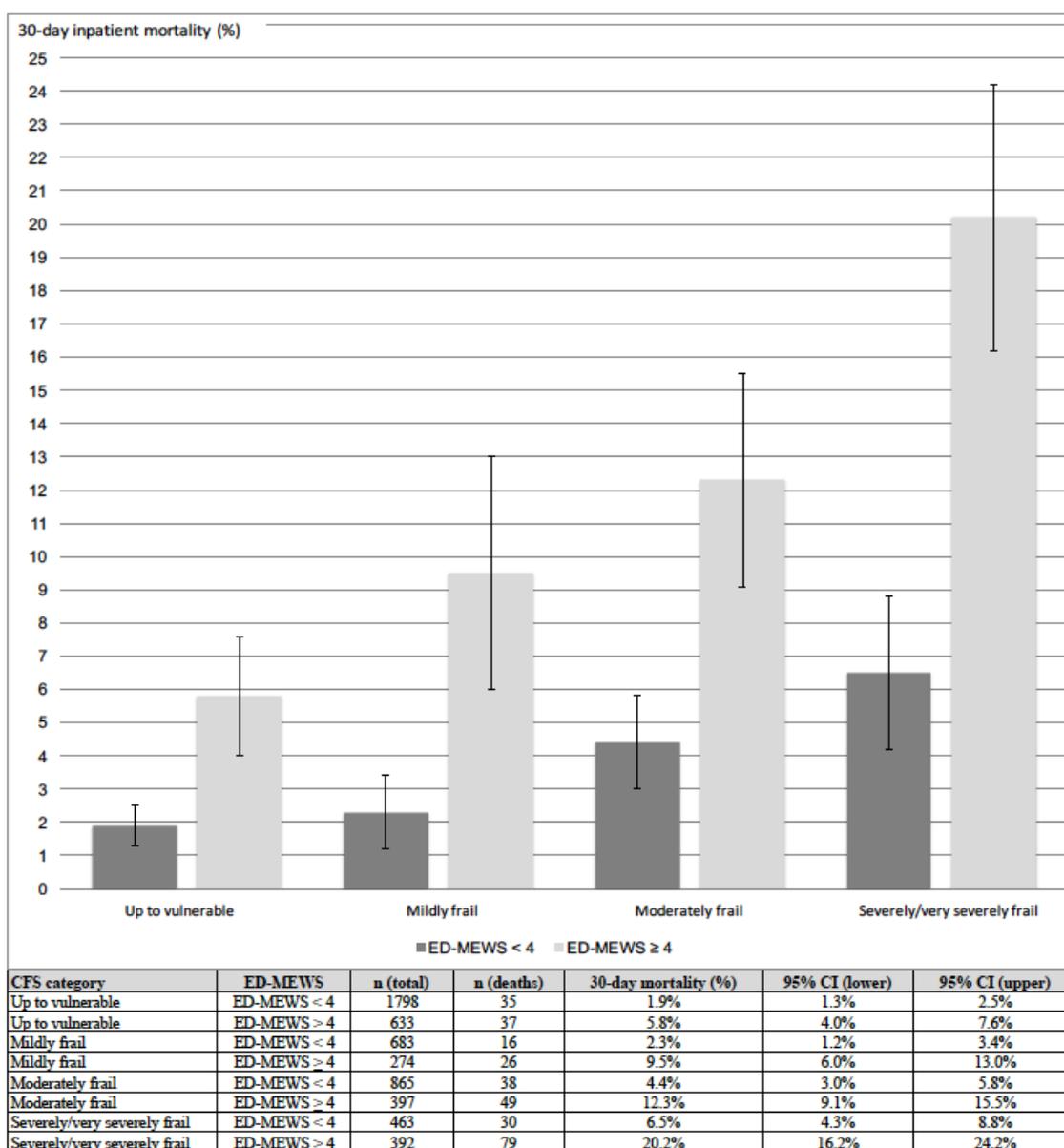
Among the 8202 first episodes, the mean age was 84.1 years (range: 75 to 105, SD 5.9), 56.5% were women, and 72.1% were discharged by a medical specialty. The median CCI was 2 (range: 0-23), 10.0% had history of dementia without current cognitive concern, and 6.3% had a current cognitive concern in the absence of known dementia.

Among the 8202 first episodes, the distribution of CFS categories was as follows: 2600 (31.7%) were up to vulnerable (CFS 1 to 4); 1021 (12.5%) mildly frail (CFS 5); 1324 (16.1%) moderately frail (CFS 6); 905 (11.0%) severely or very severely frail (CFS 7 or 8); 49 patients (0.6%) had a CFS of 9 and were excluded from the analyses, and 2303 (28.1%) had missing CFS data. In terms of initial AIS, 2325 patients (28.4%) had an ED-MEWS of 4 or more points; 5187 (63.2%) had an ED-MEWS of less than 4; and 690 (8.4%) had missing ED-MEWS data. The overall median LOS was 5 days (range: 0-209), and the 30-day inpatient mortality proportion was 6.7% (548 deaths).

The bivariate correlation between the CFS (continuous scale excluding category 9) and the ED-MEWS (continuous scale) was statistically significant, with a two-tailed Spearman's *rho* coefficient of 0.17 ( $p < 0.001$ ,  $n = 5505$  with information for both

variables, see Appendix B). Figure 1 shows the association between the CFS categories and 30-day inpatient mortality, stratified by acuity (310 deaths).

**Figure 1.** Thirty-day inpatient mortality proportion by Clinical Frailty Scale (CFS) categories and Modified Early Warning Score in the Emergency Department (ED-MEWS) status (high acuity: ED-MEWS $\geq$ 4; low acuity: ED-MEWS $<$ 4). CI: confidence interval; n: number.



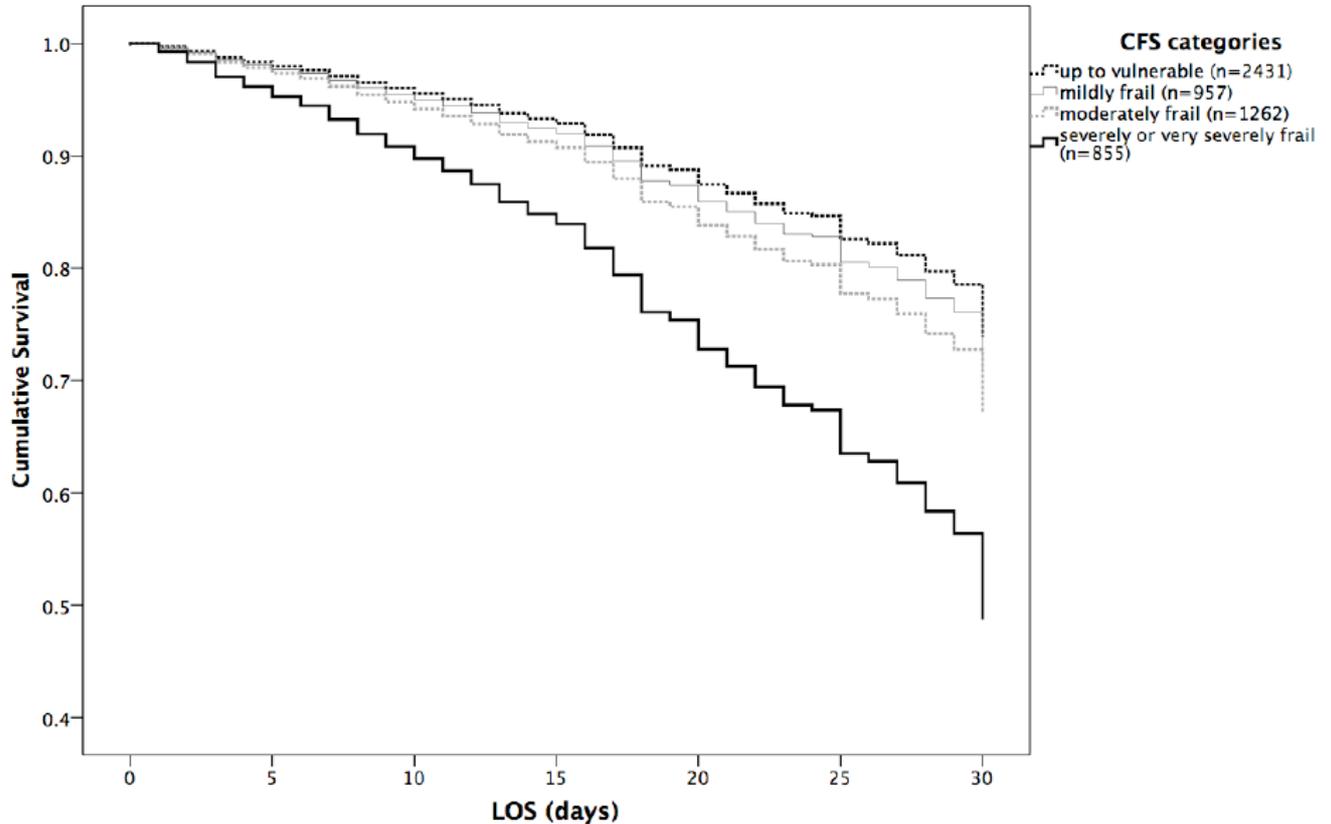
Two-hundred and thirty-eight deaths could not be included in this analysis due to missing data for either CFS or ED-MEWS. Table 1 shows the characteristics of those included in the analysis (n=5505), compared to those with missing information for either CFS or ED-MEWS (n=2697).

**Table 1.** Characteristics of patients with complete CFS and ED-MEWS information (n=5505) and comparison with those with missing CFS or ED-MEWS data (n=2697). SD: standard deviation; IQR: interquartile range; LOS: length of stay; † Independent-samples Mann-Whitney U test; ‡ Chi-squared test.

	<b>CFS and ED-MEWS not missing (n=5505)</b>	<b>Missing CFS or ED- MEWS (n=2697)</b>	<b>p for difference</b>
<b>Mean age, years (SD)</b>	84.5 (5.9)	83.3 (5.9)	<0.001 †
<b>Female gender (%)</b>	58.1	53.2	<0.001 ‡
<b>Discharged by medical specialty (%)</b>	78.7	58.5	<0.001 ‡
<b>Median CCI (IQR)</b>	2 (4)	2 (4)	0.505 †
<b>History of dementia (%)</b>	11.4	6.9	<0.001 ‡
<b>Current cognitive concern (%)</b>	7.0	4.9	<0.001 ‡
<b>Median LOS, days (IQR)</b>	6 (11)	2 (8)	<0.001 †
<b>30-day inpatient mortality % (n)</b>	5.6 (310)	8.8 (238)	<0.001 ‡
<b>Missing CFS % (n)</b>	-	87.2 (2352)	-
<b>Missing ED-MEWS % (n)</b>	-	25.6 (690)	-

In the Kaplan-Meier analysis (n=5505), the median 30-day survival times for the CFS categories were as follows: up to vulnerable: 27.1 days (95% CI: 26.4- 27.7); mildly frail: 26.3 days (95% CI: 25.2- 27.4); moderately frail: 26.5 days (95% CI: 25.8- 27.2); and severely or very severely frail: 24.3 days (95% CI: 23.3- 25.2). Judging by the lack of overlap of 95% confidence intervals, the survival of the severely or very severely frail stood out as being different from the other three CFS categories. This was visually confirmed by the age and sex adjusted survival curves, which are shown in Figure 2.

**Figure 2.** Age and sex adjusted survival curves for the total sample (n=5505), by Clinical Frailty Scale (CFS) categories.



To investigate if acuity and frailty were independent predictors of 30-day inpatient survival time while controlling for potential confounders, a Cox proportional hazards regression model was computed entering the following predictors: ED-MEWS $\geq$ 4 (no=0, yes=1), CFS categories (as an ordinal variable, with CFS 1-4 as the reference category), age (as a continuous variable), gender (male=0, female=1), discharge specialty (surgical=0, medical=1), CCI (continuous variable), history of dementia (no=0, yes=1), and current cognitive concern (no=0, yes=1). The result of this model is shown in Table 2. High acuity and CFS 7-8 were significant independent predictors of survival time. The AUC of the individual-level cumulative hazard function against 30-day inpatient mortality was 0.74 (95% CI: 0.71-0.76,  $p < 0.001$ ), suggesting acceptable discrimination [21]. The plots in Appendix C show the cumulative hazards functions for the covariates in the model, suggesting that the PH assumption was met.

**Table 2.** Results of the Cox proportional hazards regression model. CI: confidence interval. CCI: Charlson Comorbidity Index; CFS: Clinical Frailty Scale; ED-MEWS: Modified Early Warning Score in the Emergency Department.

	<b>Hazard Ratio (HR)</b>	<b>95% CI for HR (lower)</b>	<b>95% CI for HR (upper)</b>	<b>p</b>
<b>Age (years)</b>	1.04	1.02	1.07	<0.001
<b>Female sex</b>	0.93	0.74	1.18	0.565
<b>Discharge by medical specialty</b>	1.21	0.86	1.70	0.281
<b>CCI</b>	1.08	1.05	1.11	<0.001
<b>History of dementia</b>	0.49	0.35	0.69	<0.001
<b>Current cognitive concern</b>	0.89	0.62	1.27	0.510
<b>CFS 1-4 (reference)</b>	-	-	-	<0.001
<b>CFS 5</b>	1.08	0.74	1.59	0.686
<b>CFS 6</b>	1.31	0.94	1.81	0.111
<b>CFS 7-8</b>	2.10	1.52	2.92	<0.001
<b>ED-MEWS 4 or more</b>	2.87	2.27	3.62	<0.001

After missing CFS and ED-MEWS scores had been imputed using multiple imputation by chained equations, high acuity, CFS 6 and CFS 7-8 were significant independent predictors of inpatient mortality (see Appendix D).

## Discussion

To our knowledge, this study was the first to test the association between a measure of clinical frailty (vulnerability) and a measure of AIS (stressor) in predicting mortality of hospitalized older adults, in the real-world English National Health Service. Our results suggest that frailty (especially if severe or very severe) adds to acuity in the prediction of inpatient mortality in those aged 75 years or more, independently of potential confounders. It may be helpful to mainstream the measurement of frailty in acute settings in order to enable a more precise patient risk profiling at the front door; in turn, this may help form a basis for targeted interventions and more personalized care pathways [22]. For example, the identification (early during admission) of an adult aged 75 or more years with a CFS of 7 or 8 and an ED-MEWS of 4 or more, signals a high risk of inpatient mortality (20%), which could then trigger early attempts to personalize the care plan with particular attention to escalation decisions.

In keeping with our results, a previous study of all emergency admissions to an acute Irish hospital over a 12-year period showed that overall, AIS was the best independent predictor of mortality, but chronic disabling disease was an independent predictor of mortality in patients with four or more disabling conditions (i.e. the ones likely to be the frailest) [23]. Whilst chronic disabling disease relies on discharge ICD-10 codes, the CFS can be measured early during the admission, based on a clinical assessment of patients' comorbidity symptoms, and their level of physical activity and dependency on activities of daily living. Thus, the CFS is not only suitable for retrospective observational studies, but also for real life, prospective use.

In our study, the CFS and the ED-MEWS seemed to be two different entities because, although their correlation was statistically significant, the effect size of their correlation was small (Spearman's *rho* coefficient of 0.17) [24]. A previous study in NHS acute medical units reported a Spearman's *rho* coefficient of 0.23 between the CFS (1 to 9) and the National Early Warning Score (NEWS), in keeping with our result [19]. It has been said that frail patients may be 'sicker' in the acute setting because they present later to hospital (lead-time bias) or indeed, their ability to compensate for physiological derangement is impaired [19]. Attempts are often made to manage very frail people in the community, but very acute physiology can become unmanageable in the community without the appropriate resources. For example, care home patients are amongst the frailest in the community and are often referred to hospital with high acute illness severity [25].

Our study has important limitations, including its single center perspective and the relatively small number of deaths despite a large initial sample size, a problem that was significantly aggravated by missing data. The overall 30-day inpatient mortality proportion was 6.7% (548 deaths), which is comparable to overall inpatient mortality rates in England for this older age group [26,27]. However, due to our proportion of missing data, we were unable to study 238 out of 548 deaths in the database, with consequent underpower.

As suggested by results in Table 1, those with missing data were younger, more likely to be male, surgical, and to die, and less likely to be cognitively impaired. In that light, it is possible that the association between acuity and frailty and inpatient mortality

might be stronger than we reported, since our analyses truncated both the least and most vulnerable (those most likely to be discharged quickly and those most likely to die). This hypothesis is supported by the results of the sensitivity analyses, conducted after multiple imputation of missing CFS and ED-MEWS scores. When Cox proportional hazards regression was repeated in the whole patient cohort, the independent associations between both CFS and ED-MEWS score and inpatient mortality were strengthened (Appendix D).

Although 28% of our patients had missing CFS scores, we do not think that this necessarily reflects negatively on the feasibility of the CFS in the acute hospital setting. The local CQUIN scheme that mandated measurement of frailty in all older patients admitted via the emergency pathway specified that frailty had to be measured within the first 72 hours. Therefore, it was not mandatory for patients whose length of stay was <72 hours and this may have impacted on practice.

In addition, the significant proportion of missing data may be due to coding issues in the electronic database. It is possible that in some instances, variables such as the ED-MEWS score were measured but not entered in the electronic flowsheet by the attending clinicians. It is unlikely that the ED-MEWS was not measured in the 8% of patients on whom it was missing on the database. We conducted a pragmatic service evaluation and we have no means of knowing how accurate the coding of the variables used was in real clinical practice. However, undertriage of AIS is recognized in the field of Geriatric Emergency Medicine and apart from non-adherence, reasons for undertriage in older ED patients are various and complex [28,29].

Our results suggested that having history of dementia without a current cognitive concern seemed to be associated with increased survival. A possible reason for this may be that as defined in our database, current cognitive concern (without a history of dementia) may tend to capture delirium, which is often associated with higher AIS [30]. Dementia without delirium is likely to reflect lower AIS, and hence be associated with increased survival and higher LOS [20].

Despite the fact that frailty is an independent predictor of hospitalization [31], our results help understand why frailty-rating scales alone have been of limited use in risk stratifying older people in the acute setting [32]. Indeed, studies with frailty scales in acute settings must take acuity into account. AIS metrics are not usually necessary in community studies where acuity is less likely to confound the association with adverse outcomes. In the community, the identification of severe or very severe frailty (without acuity information) may also have practical implications. Firstly, community interventions may help identify remediable factors and personalize interventions aimed at reversing frailty, which if achieved may predispose patients to better outcomes when acuity strikes. In addition, there is evidence that frail patients with acute organ failure often have high rates of geriatric syndromes at hospital admission but low rates of previous participation in advance care planning activities [33]. Hence, frailty can also be a focus for personalization of care and advance care planning in the community.

## **Conclusion**

Frailty has the potential to become a powerful instrument in daily clinical practice [34], adding to acuity in the prediction of inpatient mortality in older people, independently of potential confounders. NHS hospitals may find it informative to undertake large scale assessment of frailty in older adults admitted via the emergency pathways. When combined with acute illness severity data, this process may provide hospitals with information which will help define the acute needs of the local population and aid in the development of care pathways for frail adults.

There are several validated instruments for measuring frailty and clinicians should choose one best suited to the clinical environment and/ or patient population they are working with [9]. Future prospective studies are needed to build on the findings presented here and confirm that measurement of frailty in the acute setting can help identify individuals at particular risk of poor hospital outcomes. The gold standard management for acutely hospitalized older adults is the Comprehensive Geriatric Assessment (CGA) approach [35]; and interventional trials are needed to establish whether identification of risk at the front door via routinely collected measures such as frailty and acuity may help target CGA to those who need it the most and enhance patient outcomes.

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**Disclosure statement**

The authors declare no conflict of interest.

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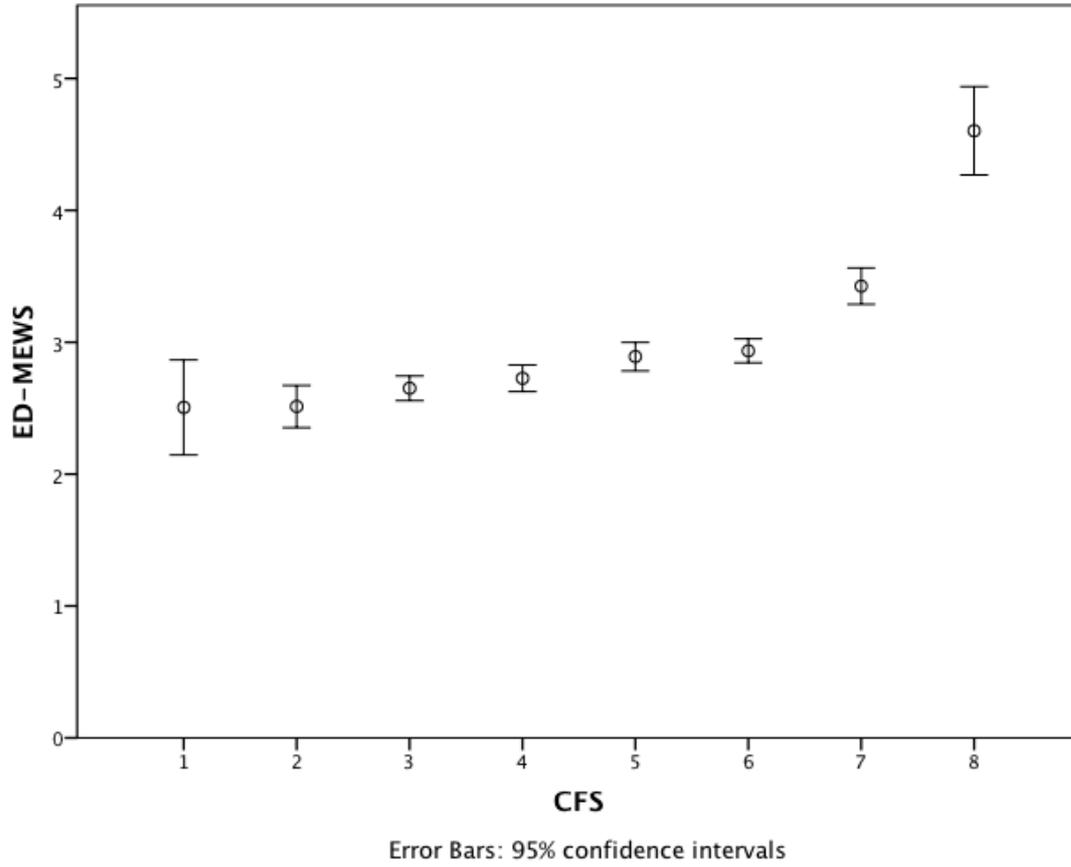
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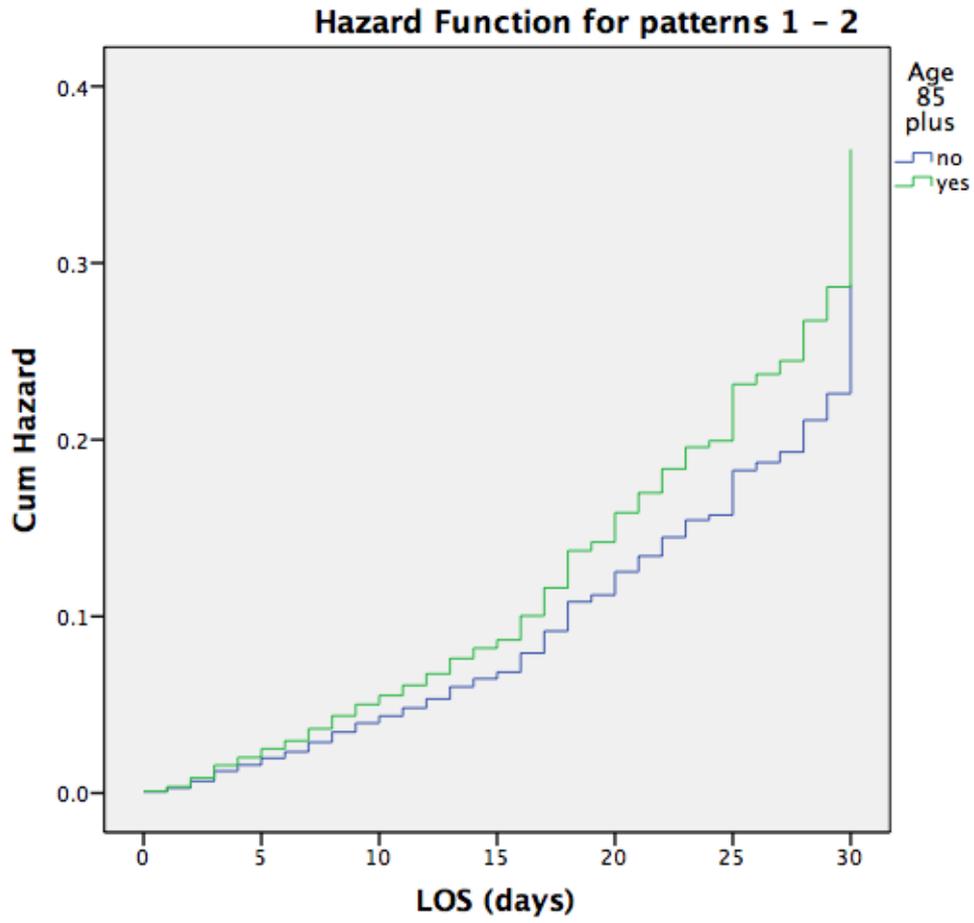
**Appendix A.** *ED-MEWS: components, scoring and escalation protocol. HR: heart rate (beats per minute); RR: respiratory rate (per minute); SBP: systolic blood pressure (mmHg); AVPU: Alert, responds to Voice, responds to Pain, Unresponsive; GCS: Glasgow Coma Scale; Temp: body temperature (degrees Celsius); minimum score = 0 points; maximum score = 15 points. Escalation trigger (i.e. immediate referral to doctor for clinical review): 4 or more points.*

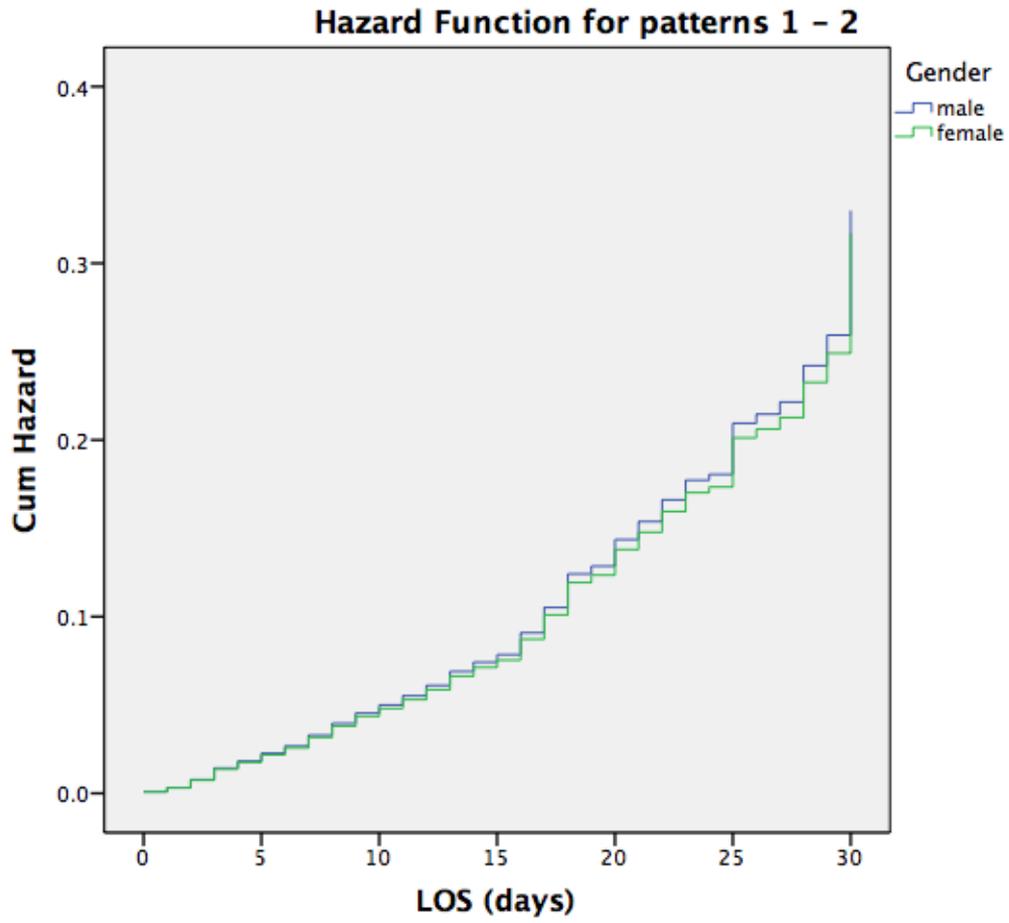
	<b>3</b>	<b>2</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>
<b>HR</b>	<40	41-50	51-60	61-90	91-110	111-129	≥130
<b>RR</b>	≤6	7-8	-	9-14	15-20	21-29	≥30
<b>SBP</b>	≤70	71-80	81-100	101-180	-	≥181	-
<b>AVPU</b>	U	P	V	A			
<b>GCS</b>				15	14	9-13	≤8
<b>Temp</b>	-	<35.0	-	35.0-38.4	-	38.5-39.0	≥39.0

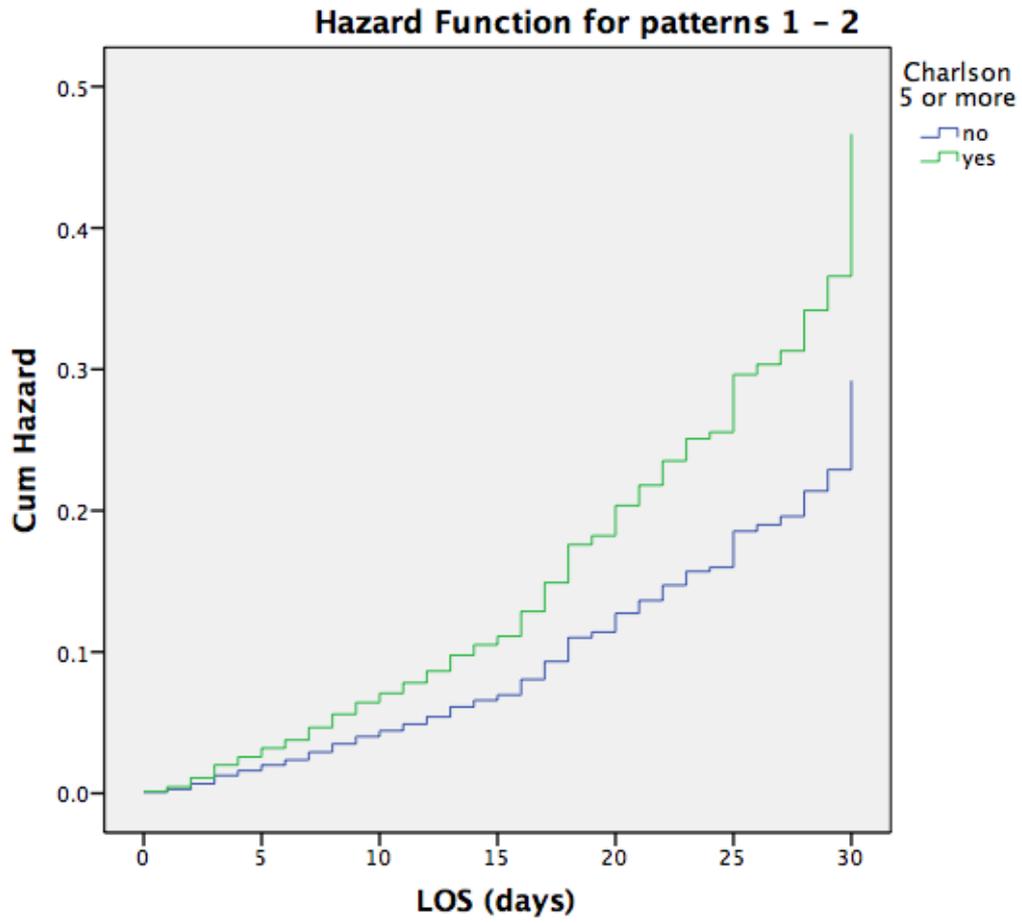
**Appendix B.** *Correlation between the CFS and the ED-MEWS (continuous variables). Two-tailed Spearman's rho correlation coefficient: 0.17 ( $p < 0.001$ ,  $n = 5505$ ).*

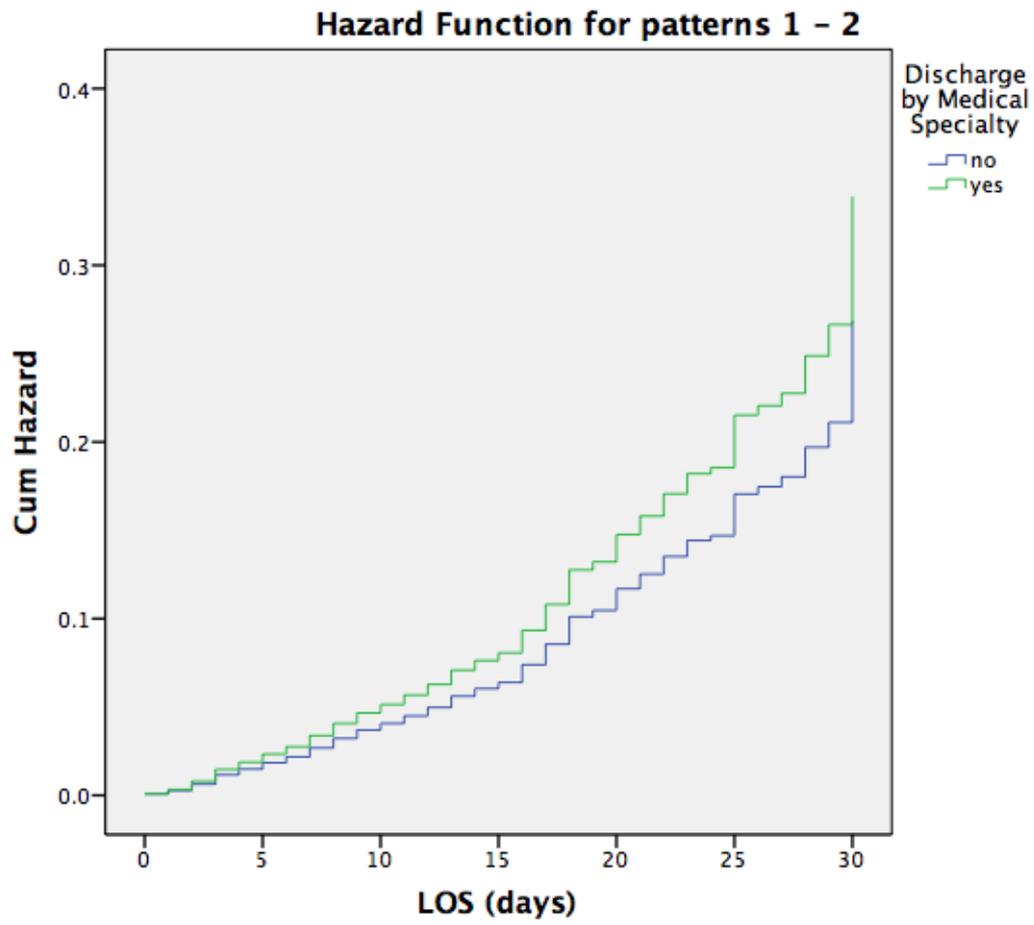


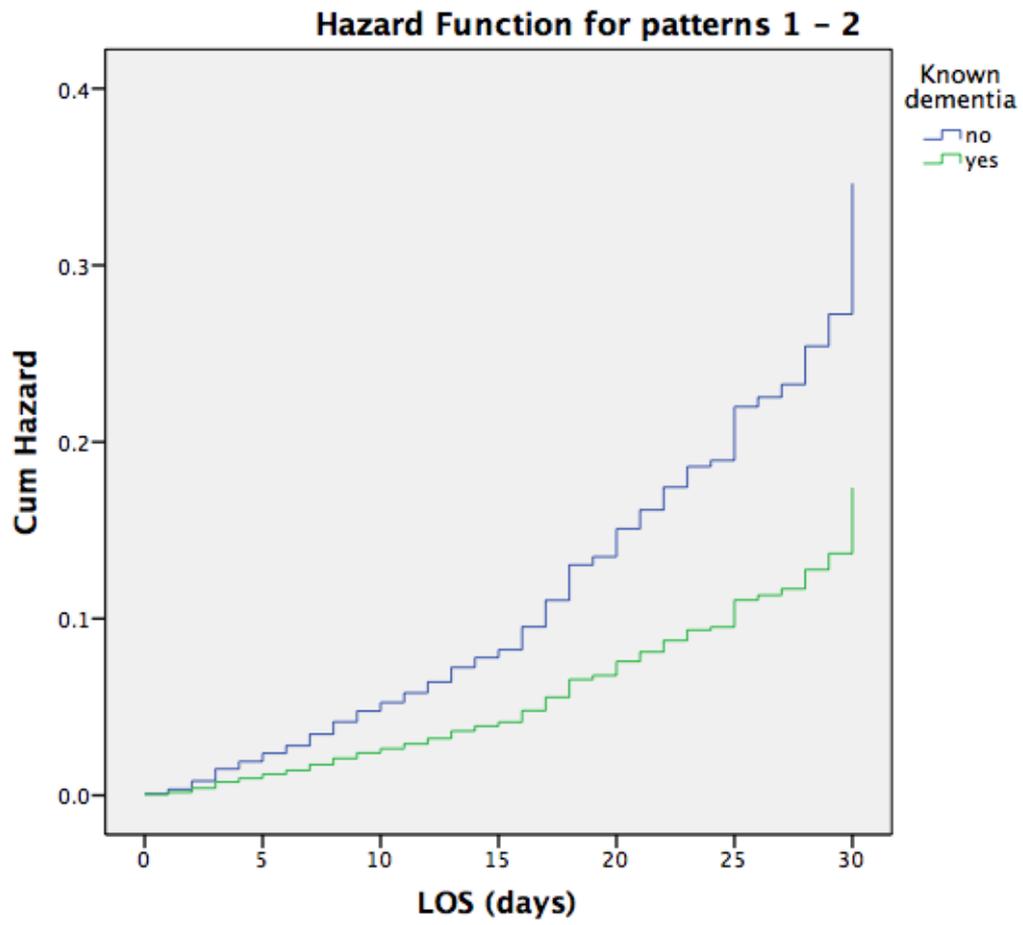
**Appendix C.** *Cumulative hazards functions for the covariates in the Cox regression model.*

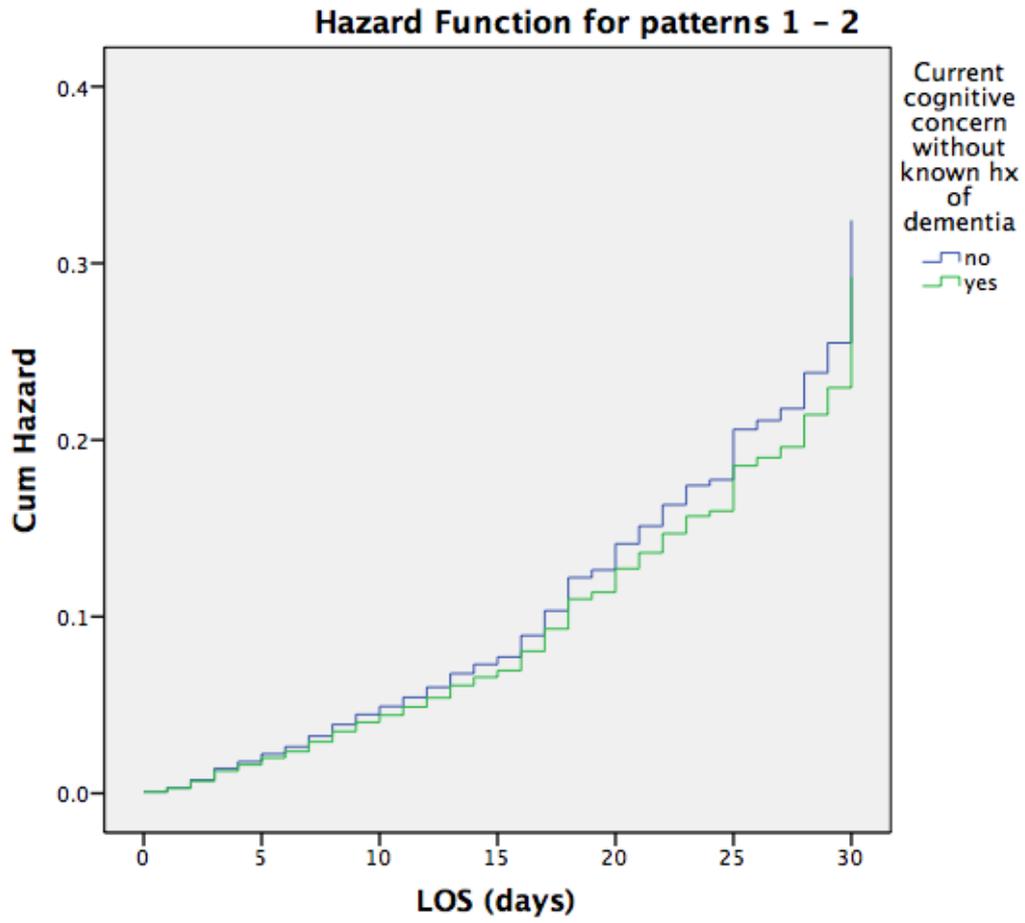


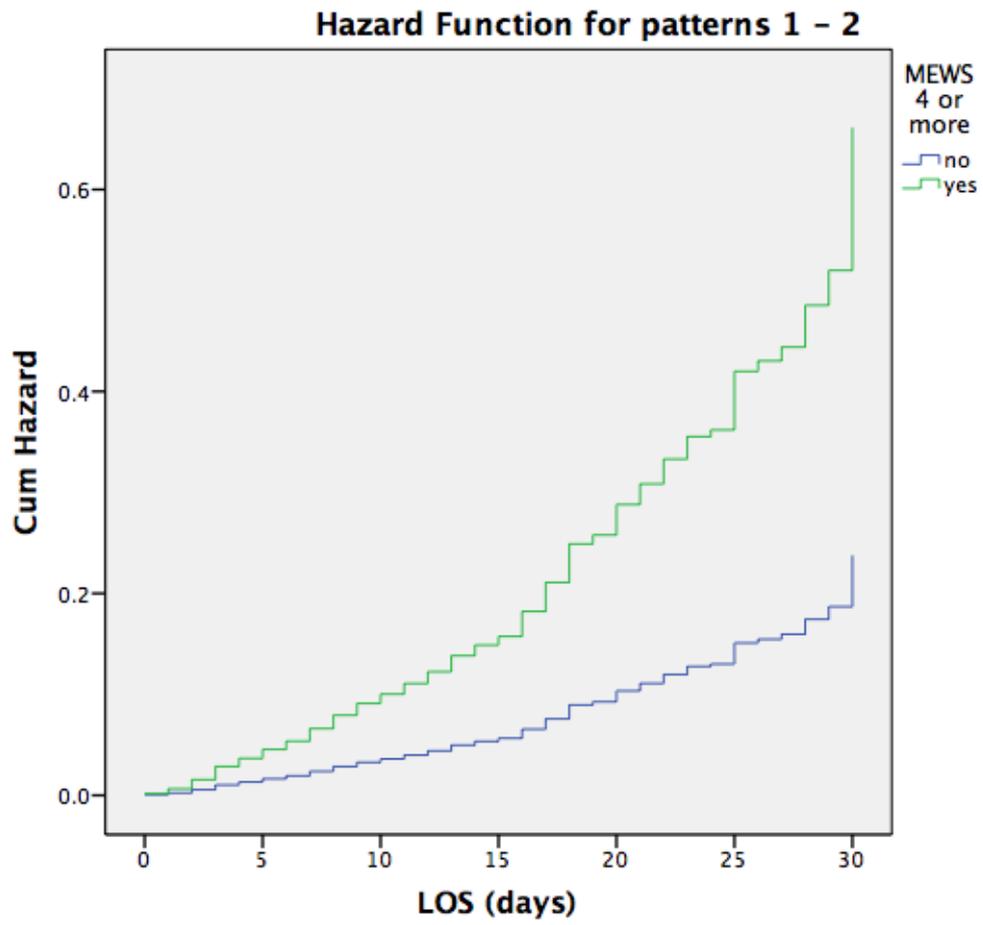


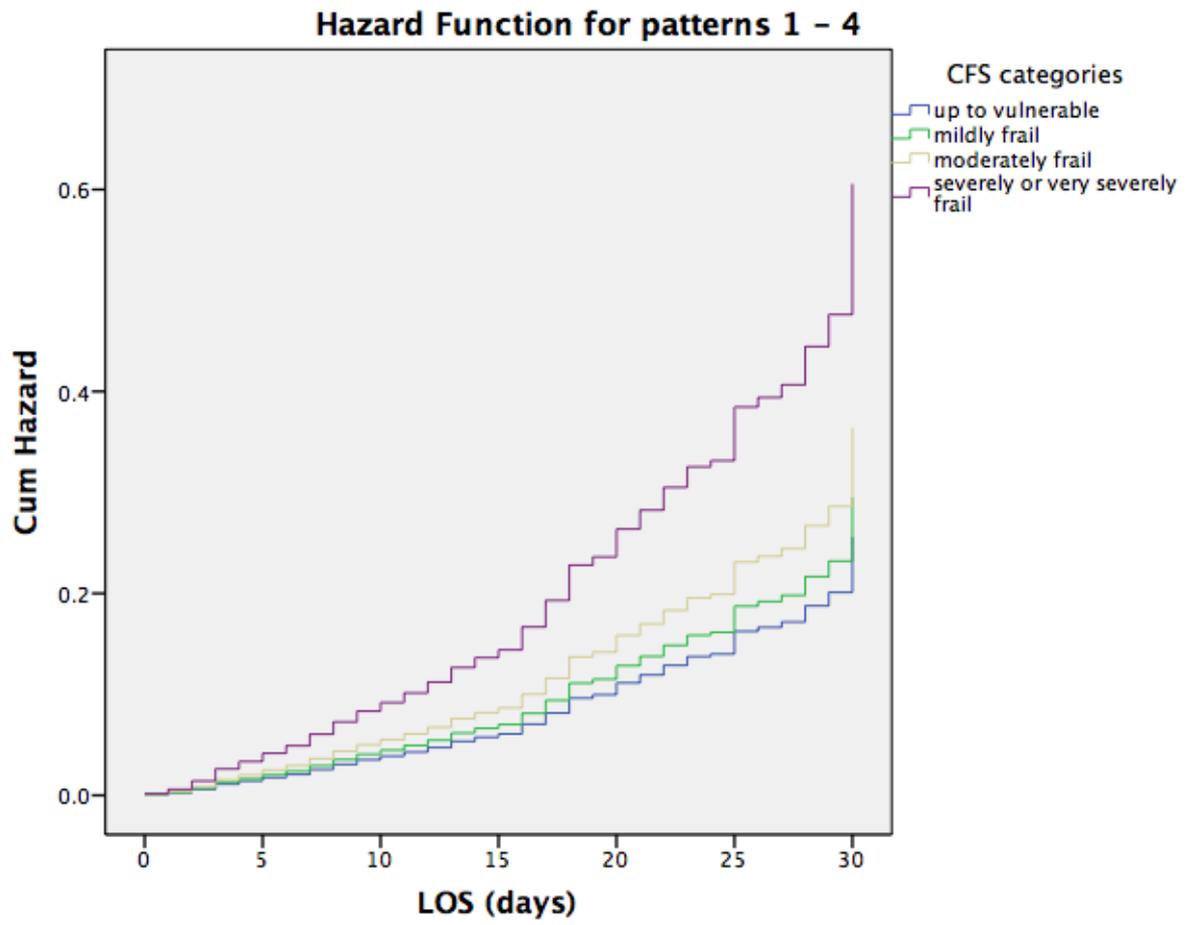












**Appendix D. Sensitivity analyses: missing data.**

Clinical Frailty Scale (CFS) and ED-MEWS scores were missing in 28.8% and 8.4% of patients respectively. Patients with missing data were younger and were more likely to be men, less cognitively impaired, discharged by a non-medical specialty, have a shorter length of stay and to die. Therefore, in order to address any potential bias introduced by the missing data, multiple imputation by chained equations was performed using Stata (version 12.0) to impute missing data in the CFS and ED-MEWS score. Multiple imputation is an efficient and appropriate method to account for missing data [1].

Ordinal logistic regression models were used to impute missing CFS and ED-MEWS scores and the dataset was restricted to 8120 patients who had complete data in all other variables. These were age, history of dementia (yes/no), current cognitive concern (yes/no), sex, Charlson Comorbidity Index and discharge by a medical specialty (yes/no). These were entered into the imputation models along with the outcome (inpatient death at 30 days), which was entered using two parameters, one indicating the event (dead) and one indicating an estimate of the cumulative hazard since baseline (Nelson-Aalen indicator). All associations to be analysed in the final analytical model were included in the imputation model. Omitting variables biases associations towards the null and can lead to erroneous conclusions [2,3].

Since nearly 30% of the CFS scores were missing, 30 imputed datasets were created and Cox proportional hazards regression was run in all 30 imputed datasets. The estimates generated were then combined using Rubin's rules [4,5].

Table: Cox proportional hazards regression model (with imputed missing data).

	Hazard Ratio	95% Confidence Intervals		p value
		Lower	Upper	
Age (years)	1.04	1.03	1.06	<0.001
Female sex	0.83	0.70	0.99	0.04
Discharge by medical specialty	0.95	0.76	1.19	0.67
CCI	1.06	1.04	1.09	<0.001
History of Dementia	0.38	0.29	0.51	<0.001
Current cognitive concern	0.52	0.38	0.71	<0.001
CFS				
1-4 (up to vulnerable)	Ref			
5 (mildly frail)	1.17	0.84	1.61	0.35
6 (moderately frail)	1.46	1.09	1.96	0.01
7-8 (severely/very sev. frail)	1.98	1.47	2.66	<0.001
ED-MEWS 4 or more	3.44	2.83	4.18	<0.001

N=8120

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