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Original Article

Frailty or multimorbidity: which matters most for the prognosis of hospitalised older adults?

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ABSTRACT

Objective: Frailty and multimorbidity frequently coexist in older adults, yet their independent and combined prognostic implications in hospitalised patients remain incompletely understood. This study aimed to investigate their prognostic contribution to six-month mortality across different operationalisations of multimorbidity and levels of frailty severity.

Methods: This observational study used prospectively collected data from adults aged ≥65 years admitted to an Acute Geriatric Unit. Frailty was assessed with the Clinical Frailty Scale (CFS), while multimorbidity was operationalised as ≥2 co-existing long-term conditions (2+LTCs), and further evaluated using the Charlson Comorbidity Index (CCI) and single disease count (SC). The primary outcome was six-month mortality. Adjusted Cox models assessed independent associations of frailty and multimorbidity with mortality, as well as their interactions.

Results: Among 2,006 patients (mean age 85.6 years; 53% female), both 2+LTCs and at least moderate frailty (CFS ≥6) were highly prevalent, each affecting 70% of participants. Overall, 445 patients (22%) died within six months after discharge. Frailty was associated with increased mortality both in the presence and absence of 2+LTCs. Across secondary models, each 1-point increase in CFS was associated with 50% higher mortality risk (all $P < 0.001$). 2+LTCs and CCI retained independent associations with mortality, whereas SC did not. A significant negative interaction was observed between frailty and CCI (P for interaction = 0.011), indicating attenuation of the prognostic contribution of weighted disease burden at higher frailty levels.

Conclusions: Frailty showed the strongest association with six-month mortality, whereas the prognostic significance of multimorbidity varied according to its operationalisation and frailty severity. These findings support broader integration of frailty assessment into prognostic stratification in hospitalised older adults.

1. Introduction

Frailty and multimorbidity represent major determinants of clinical complexity, substantially influencing healthcare use, care trajectories, and outcomes in hospitalised patients [1,2].

Frailty is defined as a clinically recognisable state of diminished physiological reserve and increased vulnerability to acute stressors [3, 4]. Conceptually, it has been described either as a biological syndrome or as the accumulation of health deficits across the life course, reflecting the complex and multidimensional nature of the condition. These different conceptual frameworks have led to the development of several assessment approaches and measurement instruments, each grounded in distinct theoretical underpinnings [1]. Multimorbidity refers to the coexistence of multiple long term conditions (LTCs) reflecting the

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cumulative burden of clinically diagnosed diseases [5]. While it is often operationalised as a simple disease count, alternative approaches incorporating disease severity have also been proposed to better capture overall disease burden [6].

Although frailty and multimorbidity are distinct constructs, both have consistently been associated with adverse clinical outcomes, including increased mortality [1,7,8]. Yet, the independent and combined prognostic roles of these two conditions in hospitalised older adults remain poorly defined. Disentangling their respective effects is challenging because they frequently coexist and partially overlap, both conceptually and methodologically, particularly when frailty is operationalised using deficit-accumulation models that incorporate disease-related variables also used to define multimorbidity [9]. Moreover, although frailty and multimorbidity may capture complementary dimensions of health, they are often evaluated as competing prognostic constructs [9]. Consequently, it remains unclear whether the prognostic impact of multimorbidity differs across levels of frailty.

To address this gap, this study aims to evaluate the independent and combined prognostic impact of frailty and multimorbidity on six-month post-discharge mortality in a large cohort of hospitalised older adults, asses whether the prognostic association of frailty was consistent across different operationalisations of multimorbidity, and determine whether the prognostic contribution of multimorbidity varied according to frailty severity.

2. Methods

2.1. Study design and participants

We conducted a retrospective analysis of prospectively collected data from patients aged ≥65 years consecutively admitted to the Acute Geriatric Unit of a tertiary hospital in Northern Italy. Patients were enrolled between March 2022 and June 2025. Written informed consent was obtained from all participants or, when appropriate, from their next of kin.

Patients who died during hospitalisation were excluded because the study outcome was post-discharge mortality. Patients discharged to hospice or home-based palliative care, or considered terminally ill, were also excluded, as their limited life expectancy had already been clinically established; their inclusion would therefore have introduced circularity into the evaluation of six-month prognosis.

The study was approved by the Lombardy Regional Ethics Committee (protocol number 001421) and conducted in accordance with the Declaration of Helsinki. Reporting followed the STROBE guidelines [10].

2.2. Data collection and clinical assessment

Data were collected by trained study personnel using an electronic case report form (eCRF) implemented through Research Electronic Data Capture (REDCap) [11]. All patients underwent a standardised Comprehensive Geriatric Assessment (CGA), including evaluation of functional status (Activities of Daily Living and Instrumental Activities of Daily Living) [12], nutritional status (serum albumin levels), and dementia diagnosis, ascertained from medical records and/or the use of acetylcholinesterase inhibitors or memantine.

Acute illness severity at admission was assessed using the National Early Warning Score 2 (NEWS–2), based on physiological parameters including respiratory rate, oxygen saturation, supplemental oxygen requirement, systolic blood pressure, heart rate, level of consciousness and body temperature [13]. Delirium was screened daily from admission to discharge using the 4AT, and confirmed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria in patients with a 4AT score ≥4 [14,15].

2.3. Frailty and multimorbidity assessment

Frailty was assessed at hospital admission using the Clinical Frailty Scale (CFS), a widely adopted and practical tool for evaluating frailty in older adults (6). Scores were assigned by experienced geriatricians based on patient's health and functional status during the two weeks preceding hospitalisation [16]. The CFS ranges from 1 (very fit) to 9 (terminally ill), with scores ≥6 corresponding to at least moderate frailty. Consistent with its original purpose, CFS scoring was based on admission CGA findings [17].

In accordance with the international Delphi consensus on multimorbidity measurement, multimorbidity was operationalised in three ways: (i) the co-occurrence of ≥2 LTCs (2+LTCs), consistent with the consensus definition; (ii) the simple count (SC) of LTCs, as an unweighted measure of disease burden; and (iii) the Charlson Comorbidity Index (CCI), as a weighted measure of disease burden. LTCs were selected according to the consensus, which recommends 24 conditions to "always include" and 35 to "usually include" [6]. The final list used in this study comprised 28 LTCs: 22 from the "always include" and 6 from the "usually include" categories, selected according to data availability and clinical relevance. The full list of the 28 LTCs and their prevalence is reported in Supplementary Table S1.

2.4. Follow-up and outcome variable

Follow-up data were retrieved by a trained data manager via the Lombardy Regional Socio-Healthcare Information System portal. For each patient, the date of hospital discharge and, where applicable, the date of death were recorded. The primary outcome was six-month post-discharge mortality, analysed both as a time-to-event variable (days from discharge to death, right-censored at 180 days) and as a binary (alive or deceased at 180 days).

2.5. Statistical analysis

Patients' demographic and clinical characteristics were summarized using descriptive statistics. Continuous variables were reported as mean (standard deviation, SD) or median (interquartile range, IQR), as appropriate, and compared using analysis of variance or Kruskal–Wallis tests. Categorical variables were presented as counts and percentages and compared using chi-square tests.

Overall survival (OS) was defined as the time from hospital discharge to death from any cause. Patients alive 180 days after discharge were censored at that time point. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test.

To explore the interplay between frailty and multimorbidity, the exposure was a combined frailty–multimorbidity variable, defined according to dichotomized frailty status and 2+LTCs. Frailty was categorized a priori using a CFS threshold of ≥6 to preserve clinical interpretability and in accordance with previous studies [18,19]. Patients were therefore classified into four mutually exclusive groups: neither frailty nor 2+LTCs (Group 1), 2+LTCs without frailty (Group 2), frailty without 2+LTCs (Group 3), and both frailty and 2+LTCs (Group 4). Univariable and multivariable Cox proportional-hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between frailty–multimorbidity groups and OS.

To further investigate the independent contribution of frailty and multimorbidity, Cox proportional hazard models were additionally fitted treating CFS as a continuous variable, to preserve statistical power and enable direct comparison of different multimorbidity operationalisations. The age-unadjusted version of the CCI was used to avoid incorporating chronological age into the multimorbidity measure, as age was considered separately in the statistical analyses [20].

Interaction analyses were conducted to assess whether the association between frailty and OS differed according to different

multimorbidity operationalisations. Multiplicative interaction terms were tested in separate Cox models for 2+LTCs, SC of LTCs, and CCI, respectively.

All multivariable models were adjusted for age, sex, delirium, serum albumin, NEWS–2, and length of hospital stay. Covariates were selected a priori on the basis of clinical relevance. Albumin values were missing in 53 patients (2.2%) and were imputed using the cohort's median value; complete-case analyses showed no meaningful differences from the primary analyses and are therefore not presented.

Model assumptions were formally evaluated. Proportional hazards assumptions were assessed using Schoenfeld residuals, the functional form of continuous predictors using penalized spline diagnostics, and multicollinearity using variance inflation factors (VIFs). When evidence of non-linearity was observed, continuous estimates were interpreted as parsimonious average effects across the observed range of values.

All statistical analyses were performed using R software, version 4.5.1 (2025-06-13) [21].

3. Results

A total of 2,708 patients were screened during the study period. After excluding patients who died during hospitalisation (n = 277), were discharged to hospice or palliative care (n = 415), or were terminally ill (CFS 9; n = 10), 2,006 patients were included in the final analysis (Supplementary Fig. S1). Six-month follow-up data were available for all participants.

Baseline characteristics of the study population are presented in Table 1. The mean age was 85.6 years (SD, 5.6), and 1,054 participants (53%) were women. The median CFS score was 6 (IQR, 5–7), and 1,408 patients (70%) had moderate-to-very severe frailty. According to the 2+LTCs definition, 1,403 patients (70%) had multimorbidity, with a median of 2 LTCs (IQR, 1–4) and a median CCI score of 2 (IQR, 1–3). Dementia was present in 734 patients (37%), while delirium during hospitalization occurred in 779 (39%). Median NEWS–2 score at admission was 2 (IQR, 0–4), mean serum albumin concentration was 33.8 g/L (SD, 4.6), and median length of hospital stay was 11 days (IQR, 8–14). Overall, 445 patients (22%) died within six months after discharge.

Overall, 246 (12%) patients were classified in Group 1, 352 (18%) in Group 2, 357 (18%) in Group 3, and 1,051 (52%) in Group 4. Six-month mortality increased progressively across groups, rising from 11% in Group 1–13%, 21%, and 28% in Groups 2, 3, and 4, respectively (P < 0.001; Supplementary Table S2). Kaplan-Meier analysis showed progressively lower survival across the frailty-multimorbidity groups, with the highest survival observed in Group 1 and the lowest in Group 4 (overall log-rank P < 0.001; Fig. 1). After adjustment, patients in Group 2 did not have an increased risk of death compared with Group 1 (adjusted Hazard Ratio [aHR], 1.14; 95% CI, 0.70–1.84; P = 0.60). By contrast, patients in Group 3 and 4 had a higher mortality risk than those in Group 1 (Group 3: aHR, 1.70; 95% CI, 1.09–2.65; P = 0.02; Group 4: aHR, 2.50; 95% CI, 1.68–3.72; P < 0.001) (Supplementary Table S3).

Table 1
Baseline characteristics of the study population.

Characteristic	Overall N = 2,006
Age, years (mean [SD])	85.6 (5.6)
Female sex, n (%)	1,054 (53)
CFS, median [IQR]	6.0 [5.0–7.0]
CFS ≥6, n (%)	1,408 (70)
Multimorbidity (2+LTCs), n (%)	1,403 (70)
Number of LTCs, median [IQR]	2.0 [1.0–4.0]
CCI, median [IQR]	2.0 [1.0–3.0]
Dementia, n (%)	734 (37)
Delirium during hospitalisation, n (%)	779 (39)
NEWS–2 score, median [IQR]	2.0 [0.0–4.0]
Serum albumin, g/L (mean [SD])	33.8 (4.6)
Length of hospital stay, days, median [IQR]	11.0 [8.0–14.0]
6-month mortality, n (%)	445 (22)

Abbreviations: SD, standard deviation; IQR, interquartile range; CFS, Clinical Frailty Scale; LTCs, long term conditions; 2+LTCs, ≥2 long term conditions; CCI, Charlson Comorbidity Index; NEWS–2, National Early Warning Score 2.

Fig. 2 shows the combined impact of frailty and multimorbidity on mortality. Frailty was consistently associated with mortality across all models, with each 1-point increase in CFS corresponding to an approximately 50% higher mortality risk (P < 0.001). Among the multimorbidity measures, both the CCI (aHR per point, 1.08; 95% CI, 1.03–1.13; P < 0.001) and 2+LTCs (aHR, 1.31; 95% CI, 1.05–1.65; P = 0.019) remained independently associated with mortality. In contrast, the SC of LTCs was not associated with mortality (aHR per condition, 1.05; 95% CI, 0.99–1.11; P = 0.098). All models were adjusted for age, sex, delirium, albumin, NEWS–2, and hospital length of stay (Supplementary Table S3).

Interaction analyses are shown in Fig. 3. No significant effect modification was observed between CFS and 2+LTCs (P for interaction = 0.545) or SC of LTCs (P for interaction = 0.808). In contrast, a significant negative interaction was identified between CFS and CCI (aHR for interaction, 0.95; 95% CI, 0.91–0.98; P for interaction = 0.011), indicating that the prognostic effect of weighted disease burden progressively attenuated at higher frailty levels.

4. Discussion

In this prospective cohort of hospitalised older adults, we examined the association of frailty and multimorbidity with six-month post-discharge mortality using three different operationalisations of multimorbidity. Across all models, frailty showed the strongest association with mortality. The association between multimorbidity and mortality differed according to both the measure of multimorbidity and the severity of frailty. While a simple count of LTCs was not associated with mortality, the presence of ≥2 LTCs showed a relatively stable association with mortality across frailty levels. By contrast, the association between CCI and mortality progressively attenuated with increasing frailty severity.

Previous studies in hospitalised older patients have mainly focused on the co-existence and interactive effect of frailty and multimorbidity on mortality. However, available evidence largely relies on administrative or claims-based datasets that may not fully capture the clinical complexity of frailty and multimorbidity [22–25]. Administrative coding systems often fail to capture disease severity and clinical heterogeneity, while electronically-derived frailty indices may incorporate overlapping disease- and disability-related variables, making it difficult to disentangle the independent contribution of frailty and multimorbidity [9,26]. These limitations may affect both prevalence estimates and interpretation of the association between these conditions. Our study, by contrast, was based on a bedside standardised CGA rather than administrative proxies, thereby providing a representation more closely aligned with the reality of acute hospital care. Interestingly, a small retrospective study conducted in hospitalised older patients using definitions similar to ours (CFS ≥ 6 for frailty and 2+LTCs for multimorbidity) found frailty to be substantially more predictive of in-hospital mortality than multimorbidity alone (positive predictive value 0.75 vs 0.39) [19]. However, the study included only 165 participants, and all frail patients were also multimorbid, precluding a clear evaluation of the independent contribution of each condition.

Our study also suggests that the prognostic value of multimorbidity depends on how it is operationalised. While frailty remained the strongest predictor of mortality, the presence of ≥2 LTCs was associated with a 31% higher risk of six-month mortality. Notably, this association appeared relatively stable across frailty levels, suggesting that multimorbidity captures a dimension of mortality risk that is not substantially modified by frailty severity. In contrast, modelling multimorbidity as SC of LTCs did not provide meaningful prognostic information. This finding

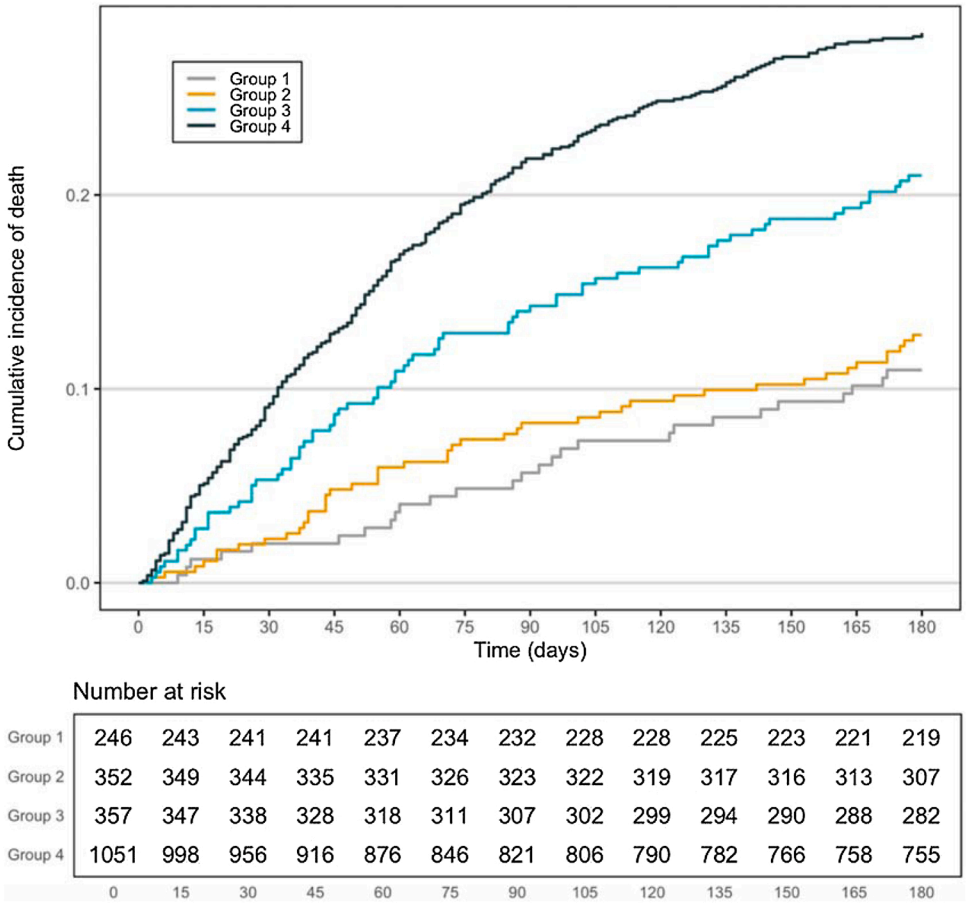


Fig. 1. Cumulative incidence of death according to frailty and multimorbidity.
Cumulative incidence of death over 180 days stratified by the combined presence of multimorbidity and frailty, defined by ≥2 long term conditions (2+LTCs) and the Clinical Frailty Scale (CFS ≥6). Group 1, neither frailty nor multimorbidity; Group 2, multimorbidity without frailty; Group 3, frailty without multimorbidity; and Group 4, both frailty and multimorbidity.

is consistent with previous methodological research highlighting the limitations of SC of LTCs as measures of multimorbidity, as they assign equal weight to all conditions and do not account for differences in disease severity, clinical burden, or prognostic relevance [27–29]. Consequently, SC of LTCs may only partially capture the heterogeneous contribution of chronic conditions to adverse outcomes. Conversely, the weighted CCI remained independently associated with mortality, suggesting that accounting for differences in disease burden improves risk stratification. However, the prognostic contribution of the CCI progressively diminished with increasing frailty severity, suggesting that, as frailty advances, impairments in physiological reserve increasingly outweigh the impact of weighted disease burden on prognosis.

Taken together, these findings help addressing one of the methodological priorities identified by the recent Delphi consensus, which highlighted the need for studies directly comparing different operationalisations of multimorbidity [6]. Our study extends this agenda by comparing these approaches while explicitly accounting for frailty and its severity. The results indicate that the prognostic value of multimorbidity depends not only on how it is operationalised but also on the degree of frailty, underscoring the importance of considering frailty when interpreting the impact of multimorbidity on mortality risk.

Our findings have important implications for both research and clinical practice. From a research perspective, our findings are consistent with the geroscience framework, in which multimorbidity and frailty are viewed as related but distinct manifestations of biological ageing [9]. While multimorbidity is increasingly understood to arise from shared and specific ageing-related biological pathways, frailty reflects the cumulative loss of physiological reserve and resilience resulting from multisystem dysregulation [30,31]. Our findings support this conceptual distinction by showing that the two constructs provide complementary rather than interchangeable prognostic information. Although further mechanistic studies are warranted, these results strengthen the rationale for investigating the biological pathways that might distinguish frailty and multimorbidity.

From a clinical perspective, our study challenges current approaches to the assessment of multimorbidity in hospitalised older adults. Different operationalisations of multimorbidity should be interpreted with caution, particularly among individuals with at least moderate frailty, where prognostic decision-making is often most relevant. In our study, the prognostic value of multimorbidity varied according to both its definition and frailty severity, whereas frailty consistently showed the strongest association with mortality across all multimorbidity operationalisations. These findings support interpreting multimorbidity within the broader context of frailty and may help explain the heterogeneity of findings across studies adopting different definitions of multimorbidity.

Decisions regarding prognosis, treatment intensity, and goals of care are frequently required in hospital settings, yet frailty remains inconsistently incorporated into routine clinical assessment. In contrast, several national and international recommendations primarily focus on multimorbidity and polypharmacy, emphasizing individualized care and the identification of patients at greatest risk of adverse outcomes [32]. Our findings support a complementary framework in which frailty serves as the cornerstone of prognostic assessment and shared clinical

Model	Variable	HR (95% CI)	P value
CFS & 2+LTCs			
	CFS, per unit	1.50 (1.35–1.68)	<0.001
	2+LTCs, yes vs no	1.31 (1.05–1.65)	0.019
CFS & SC of LTCs			
	CFS, per unit	1.51 (1.35–1.68)	<0.001
	LTCs count, per unit	1.05 (0.99–1.11)	0.098
CFS & CCI			
	CFS, per unit	1.50 (1.35–1.68)	<0.001
	CCI, per point	1.08 (1.03–1.13)	<0.001

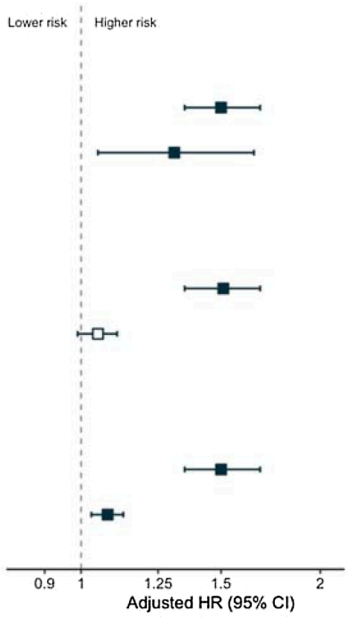


Fig. 2. Association of frailty–multimorbidity models with 6-month mortality.
Forest plot showing adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between different frailty–multimorbidity models and 6-month mortality. Models were adjusted for age, sex, delirium, albumin, NEWS–2, and hospital length of stay. Filled squares indicate statistically significant associations ($p < 0.05$), whereas open squares indicate non-significant associations.
2+LTCs = ≥2 long term conditions; SC of LTCs = single count of long term conditions; CCI = Charlson Comorbidity Index; CFS = Clinical Frailty Scale.

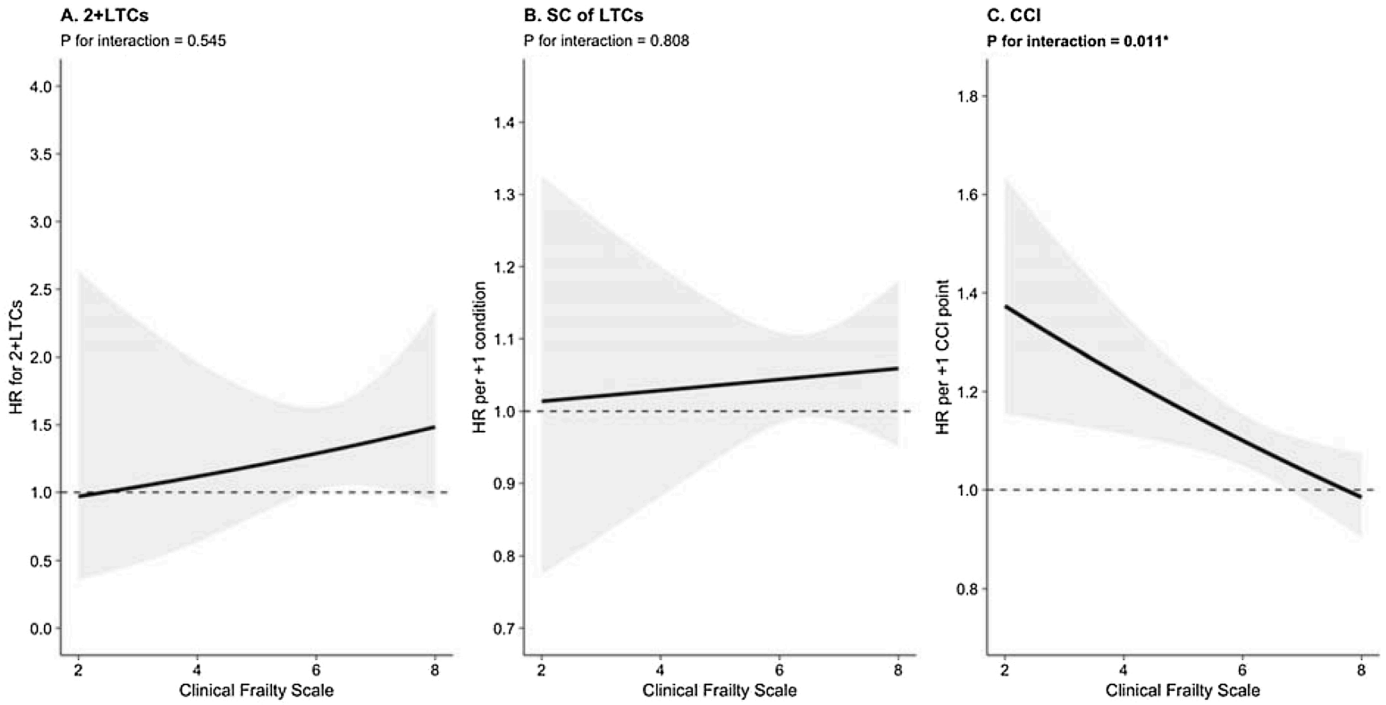


Fig. 3. Effect modification of multimorbidity measures across the frailty spectrum.
Adjusted marginal HRs for 180-day mortality across the Clinical Frailty Scale according to ≥2 long term conditions (2+LTCs) (A), single count of long term conditions (SC of LTCs) (B), and Charlson Comorbidity Index (CCI) (C). Solid lines indicate HRs and shaded areas 95% CIs. Models included CFS × multimorbidity interaction terms and were adjusted for age, sex, delirium, albumin, NEWS–2, and length of stay. *indicates a significant interaction.

decision-making, with multimorbidity provides additional context regarding disease burden and complexity. By improving prognostic stratification, frailty assessment may also help identify a timely opportunity for advance care planning, supporting discussions about care preferences and treatment goals [33]. This interpretation aligns with the aims of the Lancet Commission on Frailty, which advocates the integration of frailty assessment across medical specialties and the development of implementation frameworks to guide patient-centred care planning [34].

This study has some limitations. First, it was based on single-centre

data, potentially limiting generalisability to other clinical settings. Second, Addison's disease and inflammatory bowel disease, both categorized as "always include" conditions according to the Delphi Consensus, were unavailable in our dataset; however, given their low prevalence in similar cohorts [6], their omission is unlikely to have influenced our results. Third, multimorbidity clusters were not evaluated. However, this approach has been mainly explored in relation to long-term health trajectories rather than short- to medium-term prognostic stratification and was not an operationalisation suggested by the Delphi Consensus [6,35]. Fourth, frailty was assessed only using the CFS, and different frailty assessment tools may yield partially different associations. Nevertheless, the CFS is widely used in clinical practice, has strong prognostic performance, and minimizes conceptual overlap with the multimorbidity measures evaluated in this study [36]. Fifth, despite adjustment for major clinical confounders, residual confounding cannot be excluded because of the observational design. Finally, the high prevalence of frailty in this hospitalised geriatric cohort may limit extrapolation to younger or fitter older populations.

Our study also has several strengths. These include the large cohort of consecutively hospitalised older adults, the real-world acute geriatric setting, and the prospective bedside assessment of frailty and multimorbidity based on CGA. In addition, all analyses were adjusted for key prognostic variables spanning multiple dimensions of geriatric assessment and acute hospital care, including delirium, nutritional status (serum albumin), acute illness severity (NEWS-2), and length of hospital stay, which, to our knowledge, have rarely been available simultaneously in previous studies on this topic. Finally, by comparing multiple operationalisations of multimorbidity within the same population, our study strengthens the clinical relevance of the findings and clarifies the relative prognostic contribution of multimorbidity and frailty.

5. Conclusions

In hospitalised older adults, frailty showed a stronger association with six-month post-discharge mortality than multimorbidity across different operationalisations. While weighted disease burden retained independent prognostic value, its association with mortality progressively weakens with more severe levels of frailty. These findings support a broader integration of frailty assessment into prognostic stratification and treatment decision-making in hospitalised older adults.

CRediT authorship contribution statement

Conceptualization: AF, EE, GB; Methodology: AF, EE; Investigation: AF, EE, EP, EC, MMar, MMan; Data curation: AF, EE, EP, EC, MMar, MMan; Writing – original draft: AF, EE, CO, EP, MCF, GS, GB; Writing – review & editing: all authors. All authors reviewed and approved the final version of the manuscript.

Patient / proxy consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/proxy.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that no generative AI or AI-assisted technologies were used in the preparation of this manuscript or in the creation of figures, images, or artwork.

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Data statement

The datasets supporting the findings of this study are not publicly available but may be made available by the authors upon reasonable and justified request.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2026.101023.

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