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Standard C-Reactive Protein and Time to Death in Geriatric Outpatients: A Prognostic Signal Absent in the Oldest-Old

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Abstract

Background

Systemic inflammation is central to late-life vulnerability, and C-reactive protein (CRP) is the most widely measured inflammatory marker in routine geriatric care. However, the prognostic value of a single standard (non–high-sensitivity) CRP in ambulatory older adults, and how it varies across the ageing spectrum, is poorly defined. We examined whether baseline standard CRP is associated with the timing of death among geriatric outpatients and whether this association is modified by age, frailty and nutritional status.

Methods

In this single-centre retrospective cohort of patients aged ≥ 65 years attending a university geriatric outpatient clinic (2012–2019), the analysis was restricted to 646 decedents, with time to death as the outcome. CRP was modelled continuously, dichotomously (≥ 10 vs < 10 mg/L) and in quartiles, with Cox models adjusted for age, sex, Clinical Frailty Scale and Mini Nutritional Assessment–Short Form.

Results

Mean age was 81.7 years and 57.3% were women. Higher CRP was independently associated with a shorter time to death (adjusted hazard ratio [aHR] per 1 mg/L 1.03, 95% CI 1.01–1.05; CRP ≥ 10 mg/L aHR 1.26, 95% CI 1.02–1.55; p for trend 0.005). The association was strongly modified by age (p for interaction 0.016): aHR 1.72 (95% CI 1.24–2.40) below age 80 versus 1.02 (0.78–1.34) at ≥ 80. Discrimination was poor (time-dependent AUC 0.55–0.56; C-index 0.631), and a one-year landmark analysis attenuated the association.

Conclusions

Routine standard CRP is an independent but weak prognostic signal for the timing of death in geriatric outpatients, largely confined to those under 80 years and absent in the oldest-old. It should not be used as a stand-alone prognostic marker but interpreted in an age-aware manner within comprehensive geriatric assessment.

Background

Population ageing has made the identification of simple, accessible prognostic markers a priority in geriatric medicine. Older adults frequently present with overlapping chronic conditions, frailty, and functional decline that are inadequately captured by disease-specific models, prompting interest in biomarkers that reflect the common biological mechanisms underlying late-life vulnerability. Among

these, systemic inflammation has emerged as a central candidate. "Inflammaging"—the chronic, low-grade inflammation characteristic of biological ageing—plays a pivotal role in the pathogenesis of geriatric syndromes and physiological decline (1–3). C-reactive protein (CRP), an inexpensive and universally available acute-phase reactant, is the most widely measured inflammatory marker in routine clinical practice.

A substantial body of evidence links elevated CRP to increased mortality in older populations. However, much of this literature relies on high-sensitivity CRP (hs-CRP) assays and frames the association strictly within the subclinical inflammaging paradigm. In community cohorts, even minor hs-CRP elevations have been associated with all-cause mortality, cognitive decline, and incident frailty among older adults (4–7). Yet the prognostic behavior of standard CRP—the assay actually ordered in most clinical settings, which typically captures inflammation above the subclinical range—has received comparatively little attention. Whether standard CRP carries a dose-dependent prognostic meaning distinct from the subclinical inflammation captured by hs-CRP remains insufficiently characterised, despite its ubiquity in everyday geriatric care.

Furthermore, the prognostic value of standard CRP has been studied predominantly in acute care or hospitalised cohorts, where acute illness inflates CRP levels and compresses survival (8, 9), or in large community surveys of relatively healthy individuals (5, 6). The ambulatory geriatric outpatient—typically evaluated through a Comprehensive Geriatric Assessment (CGA) rather than during an acute decompensation—occupies an intermediate and clinically critical position that is underrepresented in the literature. In this setting, CRP is measured routinely alongside frailty and nutritional assessments, yet its independent contribution to survival beyond these established geriatric domains is not well defined (10, 11).

A critical consideration is that the prognostic strength of CRP may not be uniform across the ageing spectrum. Whether and how the prognostic value of inflammation varies with chronological age in late life remains an open question: some cohorts report that the association persists into the oldest-old, while competing risks and the high baseline mortality of this group may attenuate the discriminative power of any single biomarker (4, 12). In parallel, how the prognostic value of systemic inflammation is modified by underlying frailty status remains an area of active investigation (13). Whether inflammation acts as a uniform predictor of mortality or selectively affects older adults according to their physiological reserve has not been systematically examined in a CGA-based outpatient cohort.

Finally, conventional mortality-prediction studies often estimate the probability of death within a fixed horizon, which requires complete ascertainment of both decedents and survivors. An alternative and clinically relevant approach—particularly for prognostic counseling and end-of-life care planning—is to evaluate whether a baseline marker predicts the timing of death among those who eventually die. This time-to-death framing shifts the clinical emphasis from "who will die" to "how rapidly," directly informing decisions about treatment intensity and palliative care.

Against this background, we examined the association between baseline standard CRP and time-to-death in a well-defined cohort of geriatric outpatients. Specifically, we sought to clarify whether standard CRP provides prognostic information independent of frailty and nutritional status, and whether its prognostic relevance differs according to a patient's age and physiological reserve.

Methods

Study Design and Population

This was a retrospective cohort study conducted at the Geriatric Medicine outpatient clinic of Hacettepe University Hospital, a tertiary referral centre in Ankara, Türkiye. We reviewed records of all patients aged 65 years or older who attended the clinic between October 2012 and December 2019, during which 14,353 unique older patients were evaluated. Vital status was ascertained from the institutional electronic database. Consistent with the time-to-death design, the analysis was restricted to patients with a recorded death. After applying exclusions for data entry errors, early death within 30 days of the index visit (to minimise reverse causation from acute terminal illness), missing key variables, and a baseline CRP ≥ 20 mg/L (prespecified to exclude overt acute infection or inflammation (14, 15)), the final study cohort comprised 646 patients (Fig. 1).

Data Collection and Measurements

Baseline data were obtained from the index outpatient visit. Demographic variables (age, sex), comorbidities (hypertension, diabetes mellitus, coronary artery disease, chronic heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, malignancy, stroke/transient ischemic attack, and dementia), and the number of regular medications were recorded. Polypharmacy was defined as the regular use of five or more medications.

Frailty was assessed using the Clinical Frailty Scale (CFS) (16), analysed both as a continuous variable and dichotomized at > 4 to denote frailty. Nutritional status was assessed using the Mini Nutritional Assessment–Short Form (MNA-SF) (17, 18), analysed continuously and dichotomized at < 12 to denote being at risk of malnutrition or malnourished. Serum albumin was recorded as a continuous variable.

Serum CRP was measured by nephelometry on a Beckman Coulter IMMAGE 800 analyzer and reported in mg/L.

Exposure: CRP Quartiles

The primary exposure was baseline CRP, categorised into quartiles based on the 25th, 50th, and 75th percentiles of the cohort distribution: Q1 (< 3.0 mg/L), Q2 (3.0–<5.2 mg/L), Q3 (5.2–<10.0 mg/L), and Q4 (≥ 10.0 mg/L). Because of tied CRP values at these cut-points, group sizes were not equal (n = 132, 188,

164, and 162, respectively). The upper quartile boundary (10.0 mg/L) was adopted as the dichotomous cut-off for subsequent spline, subgroup, and sensitivity analyses.

Outcome

The primary outcome was time from the index outpatient visit to all-cause death. Follow-up was administratively censored at 36 months; patients alive at 36 months were treated as censored at that time. Hazard ratios are therefore interpreted as the relative rate of progression to death rather than the probability of death.

Statistical Analysis

Baseline characteristics were summarized across CRP quartiles. Continuous variables were expressed as median [interquartile range] and categorical variables as counts (percentages). Linear trends across quartiles were assessed using the Jonckheere–Terpstra test for continuous variables and the Cochran–Armitage test for categorical variables. Age, presented as mean ± SD, was compared across quartiles by one-way ANOVA.

The primary analysis used Cox proportional hazards regression with CRP quartiles as the exposure (Q1 as reference) and a linear trend test across quartiles. Three models were specified: Model 1, unadjusted; and Model 2, adjusted for age, sex, CFS (continuous), and MNA-SF (continuous). A third model (Model 3) additionally adjusted for variables with $p < 0.25$ in univariate analysis (hypertension, coronary artery disease, chronic kidney disease and COPD). Survival across quartiles was displayed using Kaplan–Meier curves with the log-rank test.

The proportional hazards assumption was examined using scaled Schoenfeld residuals. The dose-response relationship between continuous CRP and the hazard of death was modelled using restricted cubic splines with knots placed at standard percentiles, with departure from linearity assessed by the corresponding likelihood-ratio test. Discrimination was quantified using Harrell's C-index and time-dependent receiver operating characteristic (ROC) curves with inverse-probability-of-censoring weighting at 1, 2, and 3 years.

Effect modification was examined using the dichotomous threshold (CRP ≥ 10 vs < 10 mg/L) in prespecified subgroups defined by age, sex, frailty, nutritional status, polypharmacy, and major comorbidities. Multiplicative interaction was tested by including the relevant CRP-by-subgroup product term in the adjusted model and displayed as a forest plot.

The robustness of the primary findings was evaluated in three prespecified sensitivity analyses under alternative cohort definitions: (A) a broader cohort using a CRP upper limit of 30 mg/L and a 7-day early-death exclusion; (B) a cohort restricted to patients with CRP < 10 mg/L; and (C) a 1-year landmark cohort restricted to patients surviving at least 12 months.

All analyses were performed in R version 4.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided $p < 0.05$ was considered statistically significant.

Ethics

The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Board (approval number SBA 26/442) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective design using anonymised institutional records, the requirement for individual informed consent was waived.

Results

Cohort Characteristics

The study cohort comprised 646 deceased geriatric outpatients with a median age of 81.4 years (IQR 77.5–85.4); 370 (57.3%) were women. Compared with the overall clinic population from which it was drawn, the cohort was substantially older but had a similar sex distribution (Additional file 1). The cohort was clinically complex: median CFS was 5.0 (IQR 4.0–6.0), with 375 (58.0%) frail (CFS > 4); 300 (46.4%) were at nutritional risk (MNA-SF < 12); and 366 (56.7%) had polypharmacy. Median CRP was 5.2 mg/L (IQR 3.0–9.9).

Baseline characteristics across CRP quartiles are presented in Table 1. Increasing CRP quartile was accompanied by a clear gradient in markers of frailty and nutritional compromise: the proportion of frail patients and those at nutritional risk rose progressively across quartiles, while serum albumin declined (all p for trend < 0.05). A parallel gradient was observed for chronic kidney disease. Chronological age differed modestly across quartiles ($p = 0.022$) but without a monotonic trend (p for trend = 0.647), and sex and most comorbidities did not differ. Higher CRP was thus accompanied by greater frailty and nutritional risk without a consistent gradient in age or individual disease diagnoses.

Table 1
Baseline characteristics of the study cohort stratified by CRP quartile.

Variable	Total (n = 646)	Q1 (n = 132)	Q2 (n = 188)	Q3 (n = 164)	Q4 (n = 162)	p	p-trend
Demographics							
Age, y, mean ± SD	81.7 ± 5.3	82.5 ± 5.0	80.8 ± 4.9	82.2 ± 5.8	81.7 ± 5.4	0.022	0.647
Female, n (%)	370 (57.3)	77 (58.3)	108 (57.4)	96 (58.5)	89 (54.9)	0.912	0.610
Geriatric assessment							
CFS, median [IQR]	5.0 [4.0–6.0]	5.0 [4.0–5.0]	5.0 [4.0–6.0]	5.0 [4.0–6.0]	5.0 [4.0–5.8]	0.187	0.057
CFS > 4 (frail), n (%)	375 (58.0)	71 (53.8)	108 (57.4)	89 (54.3)	107 (66.0)	0.101	0.060
MNA-SF, median [IQR]	12.0 [9.0–14.0]	12.0 [9.0–13.0]	12.0 [10.0–14.0]	12.0 [9.8–14.0]	11.0 [8.0–13.0]	0.047	0.022
MNA-SF < 12, n (%)	300 (46.4)	56 (42.4)	80 (42.6)	74 (45.1)	90 (55.6)	0.057	0.017
Laboratory							
CRP, mg/L, median [IQR]	5.2 [3.0–9.9]	2.0 [1.5–2.2]	4.0 [3.0–4.6]	7.0 [6.0–8.0]	12.6 [10.0–16.0]	—	—
Albumin, g/dL, median [IQR]	4.0 [3.6–4.2]	4.1 [3.8–4.3]	4.0 [3.7–4.2]	3.9 [3.6–4.1]	3.8 [3.5–4.0]	< 0.001	< 0.001
Comorbidities, n (%)							

Data are mean ± SD (age), median [IQR] (other continuous variables), or n (%). p: one-way ANOVA (age), Kruskal–Wallis (other continuous variables), or chi-square (categorical). p-trend: Jonckheere–Terpstra (continuous) or Cochran–Armitage (categorical). CKD defined as eGFR < 45 mL/min/1.73 m².

Cumulative deaths reflect the distribution of death timing within the decedent cohort, not mortality probability in the source population. CRP quartile boundaries (25th/50th/75th percentiles of the study cohort): Q1 < 3.0, Q2 3.0–<5.2, Q3 5.2–<10.0, Q4 ≥ 10.0 mg/L (right-open intervals); group sizes differ owing to tied values. CRP, C-reactive protein; CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment–Short Form; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack; IQR, interquartile range; SD, standard deviation.

Variable	Total (n = 646)	Q1 (n = 132)	Q2 (n = 188)	Q3 (n = 164)	Q4 (n = 162)	p	p-trend
Demographics							
Hypertension	460 (71.2)	91 (68.9)	131 (69.7)	117 (71.3)	121 (74.7)	0.681	0.242
Diabetes mellitus	230 (35.6)	44 (33.3)	68 (36.2)	50 (30.5)	68 (42.0)	0.167	0.244
Coronary artery disease	276 (42.7)	47 (35.6)	80 (42.6)	80 (48.8)	69 (42.6)	0.158	0.162
Chronic heart failure	184 (28.5)	32 (24.2)	48 (25.5)	54 (32.9)	50 (30.9)	0.260	0.095
Atrial fibrillation	59 (9.1)	11 (8.3)	18 (9.6)	17 (10.4)	13 (8.0)	0.876	0.948
COPD	93 (14.4)	13 (9.8)	25 (13.3)	24 (14.6)	31 (19.1)	0.147	0.023
CKD (eGFR < 45)	133 (20.6)	22 (16.7)	28 (14.9)	45 (27.4)	38 (23.5)	0.015	0.020
Malignancy	83 (12.8)	14 (10.6)	19 (10.1)	23 (14.0)	27 (16.7)	0.244	0.059
Stroke/TIA	47 (7.3)	14 (10.6)	11 (5.9)	9 (5.5)	13 (8.0)	0.302	0.490
Dementia	181 (28.0)	49 (37.1)	39 (20.7)	52 (31.7)	41 (25.3)	0.007	0.230
Medications							
No. of medications, median [IQR]	5.0 [3.0–7.0]	4.0 [3.0–6.0]	5.0 [3.0–7.0]	6.0 [3.0–8.0]	5.0 [3.0–7.8]	0.081	0.103
Polypharmacy (≥ 5), n (%)	366 (56.7)	65 (49.2)	112 (59.6)	98 (59.8)	91 (56.2)	0.234	0.326

Data are mean ± SD (age), median [IQR] (other continuous variables), or n (%). p: one-way ANOVA (age), Kruskal–Wallis (other continuous variables), or chi-square (categorical). p-trend: Jonckheere–Terpstra (continuous) or Cochran–Armitage (categorical). CKD defined as eGFR < 45 mL/min/1.73 m².

Cumulative deaths reflect the distribution of death timing within the decedent cohort, not mortality probability in the source population. CRP quartile boundaries (25th/50th/75th percentiles of the study cohort): Q1 < 3.0, Q2 3.0–<5.2, Q3 5.2–<10.0, Q4 ≥ 10.0 mg/L (right-open intervals); group sizes differ owing to tied values. CRP, C-reactive protein; CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment–Short Form; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack; IQR, interquartile range; SD, standard deviation.

Variable	Total (n = 646)	Q1 (n = 132)	Q2 (n = 188)	Q3 (n = 164)	Q4 (n = 162)	p	p-trend
Demographics							
Cumulative deaths, n (%)							
Deaths within 1 year	171 (26.5)	28 (21.2)	46 (24.5)	45 (27.4)	52 (32.1)	0.173	0.027
Deaths within 2 years	318 (49.2)	55 (41.7)	89 (47.3)	81 (49.4)	93 (57.4)	0.054	0.007
Deaths within 3 years	461 (71.4)	84 (63.6)	130 (69.1)	123 (75.0)	124 (76.5)	0.058	0.008

Data are mean ± SD (age), median [IQR] (other continuous variables), or n (%). p: one-way ANOVA (age), Kruskal–Wallis (other continuous variables), or chi-square (categorical). p-trend: Jonckheere–Terpstra (continuous) or Cochran–Armitage (categorical). CKD defined as eGFR < 45 mL/min/1.73 m².

Cumulative deaths reflect the distribution of death timing within the decedent cohort, not mortality probability in the source population. CRP quartile boundaries (25th/50th/75th percentiles of the study cohort): Q1 < 3.0, Q2 3.0–<5.2, Q3 5.2–<10.0, Q4 ≥ 10.0 mg/L (right-open intervals); group sizes differ owing to tied values. CRP, C-reactive protein; CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment–Short Form; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack; IQR, interquartile range; SD, standard deviation.

CRP and Time to Death

Kaplan–Meier analysis demonstrated progressively shorter survival across ascending CRP quartiles (log-rank p = 0.023, p for trend = 0.002; Fig. 2). In quartile-based Cox regression (Table 2), the hazard of death increased monotonically across quartiles. After adjustment for age, sex, frailty, and nutritional status, each 1 mg/L increment in CRP was associated with a higher hazard of death (aHR 1.03, 95% CI 1.01–1.05), a CRP ≥ 10 mg/L carried an elevated hazard (aHR 1.26, 95% CI 1.02–1.55), and the highest quartile retained a significantly elevated hazard relative to the lowest (Q4 vs Q1 aHR 1.49, 95% CI 1.12–1.96), with a significant linear trend (p-trend = 0.005). Additional adjustment for comorbidities did not materially alter the estimates and did not improve model fit (likelihood-ratio p > 0.05).

Table 2
Cox proportional-hazards models for the association between baseline CRP and time to death.

CRP parameterization	Events/n	Model 1 HR (95% CI), p	Model 2 HR (95% CI), p[a]	Model 3 HR (95% CI), p[a]
Continuous (per 1 mg/L)	461/646	1.03 (1.01–1.05) p = 0.003	1.03 (1.01–1.05) p = 0.007	1.03 (1.01–1.05) p = 0.014
CRP ≥ 10 vs < 10 mg/L	461/646	1.28 (1.04–1.57) p = 0.019	1.26 (1.02–1.55) p = 0.031	1.24 (1.00-1.53) p = 0.046
Quartiles				
Q1 (< 3.0 mg/L)	84/132	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2 (3.0–<5.2 mg/L)	130/188	1.16 (0.88–1.53) p = 0.284	1.22 (0.93–1.61) p = 0.159	1.21 (0.92–1.60) p = 0.174
Q3 (5.2–<10.0 mg/L)	123/164	1.34 (1.02–1.77) p = 0.037	1.31 (0.99–1.73) p = 0.061	1.26 (0.95–1.68) p = 0.107
Q4 (≥ 10.0 mg/L)	124/162	1.50 (1.14–1.98) p = 0.004	1.49 (1.12–1.96) p = 0.005	1.45 (1.09–1.92) p = 0.010
p for trend		0.002	0.005	0.012

Hazard ratios represent the relative rate of progression to death among decedents. Model 1: unadjusted. [a]*Model 2: adjusted for age, sex, Clinical Frailty Scale (continuous), and Mini Nutritional Assessment–Short Form (continuous).* [a]*Model 3: adjusted for variables with p < 0.25 in univariate analysis (age, sex, CFS, MNA-SF, hypertension, coronary artery disease, CKD* (eGFR < 45)*, COPD). The C-index (0.631) refers to the adjusted continuous-CRP model. CRP, C-reactive protein; HR, hazard ratio; CI, confidence interval.*

Dose-Response and Discrimination

Restricted cubic spline modelling showed an approximately linear, monotonically increasing relationship between CRP and the hazard of death, without significant departure from linearity (non-linearity p = 0.867; Additional file 2). This independent association was not matched by discriminative ability. As a stand-alone marker, CRP barely exceeded chance, with unadjusted time-dependent areas under the curve of 0.556, 0.550, and 0.561 at one, two, and three years (Additional file 3); the fuller model combining CRP with age, sex, frailty, and nutritional status reached only a modest Harrell's C-index of 0.631. A robust population-level association thus coexisted with limited ability to order individual survival times.

Effect Modification by Age

The association between CRP and time to death was strongly modified by age (p for interaction = 0.016; Fig. 3). Among patients younger than 80 years, a CRP ≥ 10 mg/L was associated with a substantially higher hazard of death (aHR 1.72, 95% CI 1.24–2.40), whereas among those aged 80 years or older the association was null (aHR 1.02, 95% CI 0.78–1.34; p for interaction = 0.016). A similar pattern was observed by frailty status (p for interaction = 0.075): the association was present among frail patients but not among non-frail patients, although this interaction did not reach conventional significance. No significant interaction was detected for sex, nutritional status, polypharmacy, or major comorbidities; several subgroups showed directionally consistent but non-significant point estimates and are reported as hypothesis-generating (Fig. 3).

Sensitivity Analyses

The primary findings were robust across the prespecified sensitivity cohorts (Additional file 4). The association persisted under a broader inclusion definition (Sensitivity A; CRP ≥ 10 mg/L aHR 1.37, 95% CI 1.15–1.63). In the cohort restricted to CRP < 10 mg/L (Sensitivity B), the continuous association was attenuated and no longer significant (aHR 1.05 per 1 mg/L, 95% CI 0.99–1.10). In the one-year landmark cohort (Sensitivity C), the association was attenuated and no longer reached significance (CRP ≥ 10 mg/L aHR 1.19, 95% CI 0.91–1.56).

Discussion

In this retrospective cohort of deceased geriatric outpatients, baseline standard CRP was independently associated with the timing of death. The hazard of death rose across CRP quartiles, with the highest quartile (≥ 10.0 mg/L) retaining a significantly elevated hazard after adjustment for age, sex, frailty, and nutritional status, following a linear dose-response relationship. The effect was not uniform: it was present in patients younger than 80 years but absent in the oldest-old, with a directionally similar though non-significant pattern by frailty status. Despite this association, CRP discriminated poorly between earlier and later death. Standard CRP is therefore a genuine but modest prognostic signal whose relevance is mainly modified by age.

The prognostic signal emerged from standard CRP above the subclinical range, not from the low-grade elevations central to inflammaging. Most prior evidence linking CRP to mortality in older adults derives from high-sensitivity assays, with thresholds as low as 3 mg/L carrying prognostic weight (4, 6). Our data differ: the hazard was relatively flat across the lower three quartiles and rose only in the highest, whose boundary (10.0 mg/L) lies well above the subclinical, inflammaging range in which hs-CRP is typically interpreted, at a level more consistent with clinically relevant inflammation (8, 19). The association also lost significance when the cohort was restricted to CRP below 10 mg/L and attenuated in the one-year landmark analysis. These observations suggest that standard CRP here reflects an acute-to-subacute inflammatory burden distinct from inflammaging.

The prognostic effect of CRP was modified by age and, less strongly, by frailty, being present in younger and frail patients but absent in the oldest-old. This pattern contrasts with reports that CRP retains prognostic value at advanced ages: in the Leiden 85-plus Study CRP remained an independent predictor, albeit with a small effect size (12), and in a Chinese oldest-old cohort hs-CRP predicted mortality even beyond age 80 (4). Even within the high-sensitivity CRP literature the age pattern is inconsistent: other cohorts report that the mortality association weakens at older ages, with a substantially higher hazard below age 65 than above it (20). Our findings add a dimension to this debate, since the signal we observed arose from standard rather than high-sensitivity CRP; both the assay range and the age distribution differ from these cohorts, and our null association in the oldest-old may reflect either a genuine biological attenuation or a structural feature of our design. In our oldest-old subgroup, deaths were heavily concentrated within the first three years of follow-up, compressing the distribution of survival times. Because our outcome is the timing of death rather than its occurrence, this compression leaves little variability for any single marker to stratify. Our null finding in the oldest-old may therefore reflect this structural compression rather than a true biological absence of association.

The age and frailty interactions point in the same direction, towards a stronger CRP effect where reserve is reduced. Although the effect modification by frailty did not reach conventional significance (p for interaction = 0.075), its direction and magnitude paralleled the age finding. This is biologically plausible: systemic inflammation and frailty are closely and bidirectionally linked (21, 22), such that an inflammatory marker may carry greater prognostic weight in those whose physiological reserve is already compromised.

CRP was independently associated with time to death but discriminated poorly, with a modest C-index and time-dependent ROC areas below 0.60 for CRP alone. This dissociation between association and discrimination is well documented: CRP is an independent mortality predictor that nonetheless adds little to conventional risk models, whether in older cohorts (23), in community studies of all-cause mortality (24), or in large-scale cardiovascular meta-analyses where it improves the C-index by only a few thousandths (25). A robust population-level association can thus coexist with negligible individual-level discrimination, because association and prediction answer different questions. CRP should therefore not be used as a standalone prognostic test; rather, like other routine markers, it contributes to risk prediction mainly as one component of multidomain tools (26), its value lies in flagging an inflammatory burden that tracks with frailty and malnutrition rather than in predicting who will die sooner.

This study addressed the timing of death rather than its occurrence. Because the cohort comprised patients who had died, the estimates describe the relative rate of progression to death—a question that is clinically pertinent when patients are already recognised as high-risk and the actionable issues are the intensity of treatment, the timing of advance care planning, and the closeness of follow-up (27). A routine marker that signals a faster trajectory—particularly in younger-old and frail patients—could contribute to these decisions, though as a supportive element within comprehensive geriatric assessment rather than a decisive one.

Strengths include the focus on an underexamined outpatient setting, the use of a routinely available marker, and a rigorous analytical approach combining quartile modelling, restricted cubic splines, time-dependent discrimination, subgroup testing, and sensitivity analyses. Limitations must also be noted. First, the cohort included only patients who died and no survivors; the findings therefore describe the timing of death among decedents and cannot be extrapolated to mortality risk in the general outpatient population. Second, the study was single-centre and retrospective, limiting generalisability and allowing unmeasured confounding. Third, CRP was measured once, precluding assessment of its trajectory (28). Fourth, the attenuation of the association in the one-year landmark analysis indicates that part of the observed signal reflects occult illness already present at baseline rather than a long-term effect of inflammation; the prognostic value of CRP in this setting is therefore partly that of a short-term marker. Fifth, despite excluding CRP ≥ 20 mg/L, residual subclinical acute processes cannot be excluded. Finally, the analytic cohort was older than the source population, reflecting the selection inherent to the design.

Conclusions

In geriatric outpatient practice, an elevated standard CRP (particularly ≥ 10 mg/L) should not be interpreted as a standalone predictor of survival but may signal an inflammatory burden warranting attention to coexisting frailty and malnutrition. Its prognostic relevance appears greatest in younger-old (and possibly in frail patients, though this did not reach significance), where it may support but not replace clinical judgement in decisions about treatment intensity and care planning. Future prospective studies in unselected cohorts that include survivors are needed to determine whether these associations extend to mortality prediction, and longitudinal measurements may clarify whether inflammatory trajectories outperform single values.

Abbreviations

CRP
C-reactive protein
hs-CRP
high-sensitivity C-reactive protein
CGA
comprehensive geriatric assessment
CFS
Clinical Frailty Scale
MNA-SF
Mini Nutritional Assessment–Short Form
aHR
adjusted hazard ratio
CI
confidence interval
ROC

receiver operating characteristic
AUC
area under the curve
IQR
interquartile range
CKD
chronic kidney disease
COPD
chronic obstructive pulmonary disease
eGFR
estimated glomerular filtration rate
TIA
transient ischaemic attack.

Declarations

Ethics approval and consent to participate.

The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Board (approval number SBA 26/442) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective design using anonymised institutional records, the requirement for individual informed consent was waived by the same board.

Consent for publication.

Not applicable.

Competing interests.

The authors declare that they have no competing interests.

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Author Contribution

OT conceived and designed the study, performed the statistical analysis and drafted the manuscript. SC and ZÖÖ contributed to the methodology and analysis. CK, MP, İAN, ÖÖ and DC collected and curated the data. AOB and MGH contributed to the methodology and critically revised the manuscript. ME, CB, BBD,

MC and MGH supervised the study and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Not applicable.

Availability of data and materials.

The datasets generated and/or analysed during the current study are not publicly available due to institutional data-protection restrictions but are available from the corresponding author on reasonable request.

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Figures

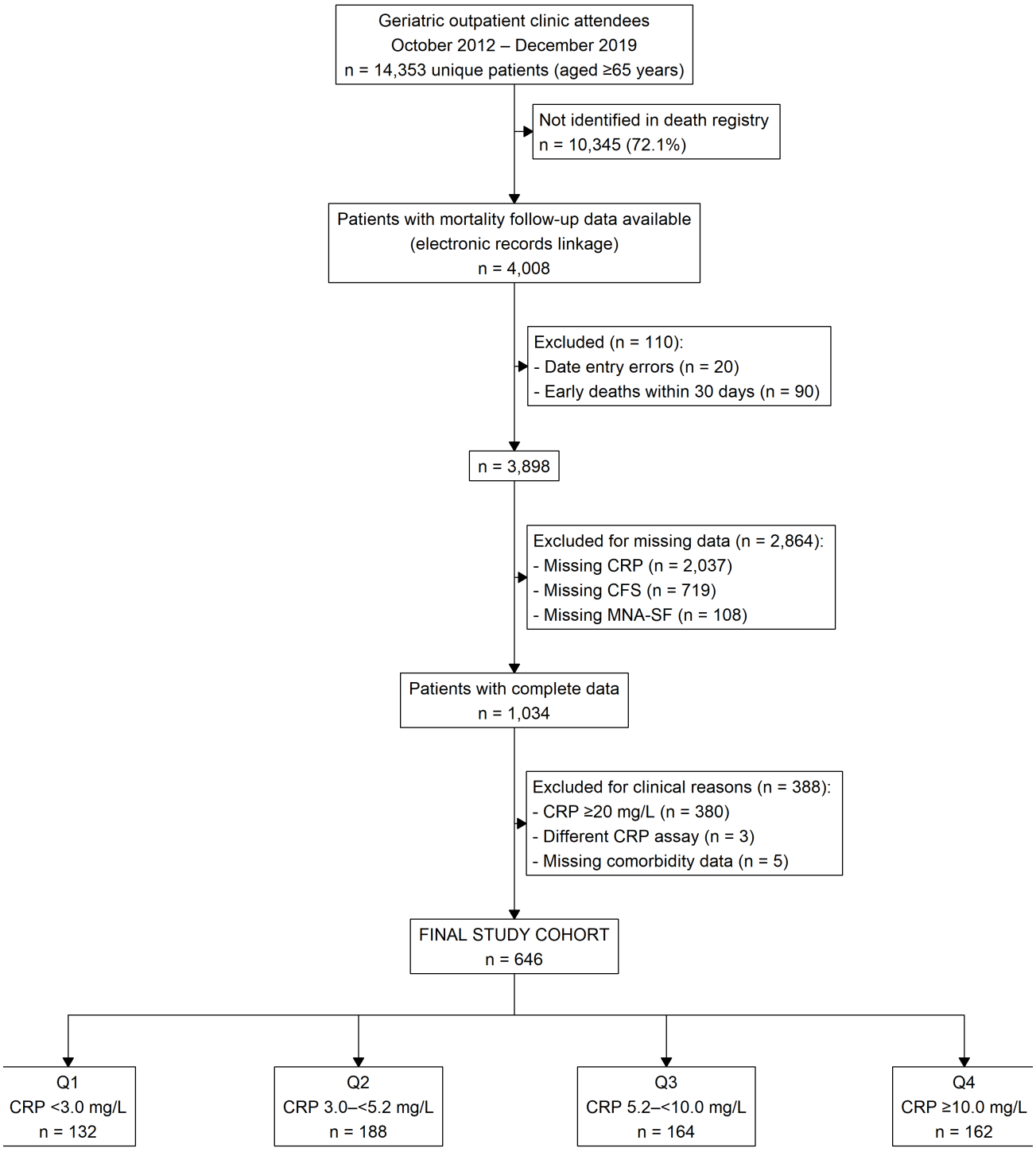


Figure 1

Flow of participants through the study. From 14,353 unique patients aged ≥65 years who attended the geriatric outpatient clinic between October 2012 and December 2019, sequential exclusions (patients not recorded as deceased, consistent with the decedents-only, time-to-death design; data-entry errors and death within 30 days of the index visit; missing key covariates; and baseline CRP ≥20 mg/L or a non-standard assay) yielded the final analytic cohort of 646 decedents, stratified into CRP quartiles Q1 (<3.0

mg/L, n = 132), Q2 (3.0–<5.2 mg/L, n = 188), Q3 (5.2–<10.0 mg/L, n = 164) and Q4 (≥10.0 mg/L, n = 162). CRP, C-reactive protein; CFS, Clinical Frailty Scale; MNA-SF, Mini Nutritional Assessment–Short Form.

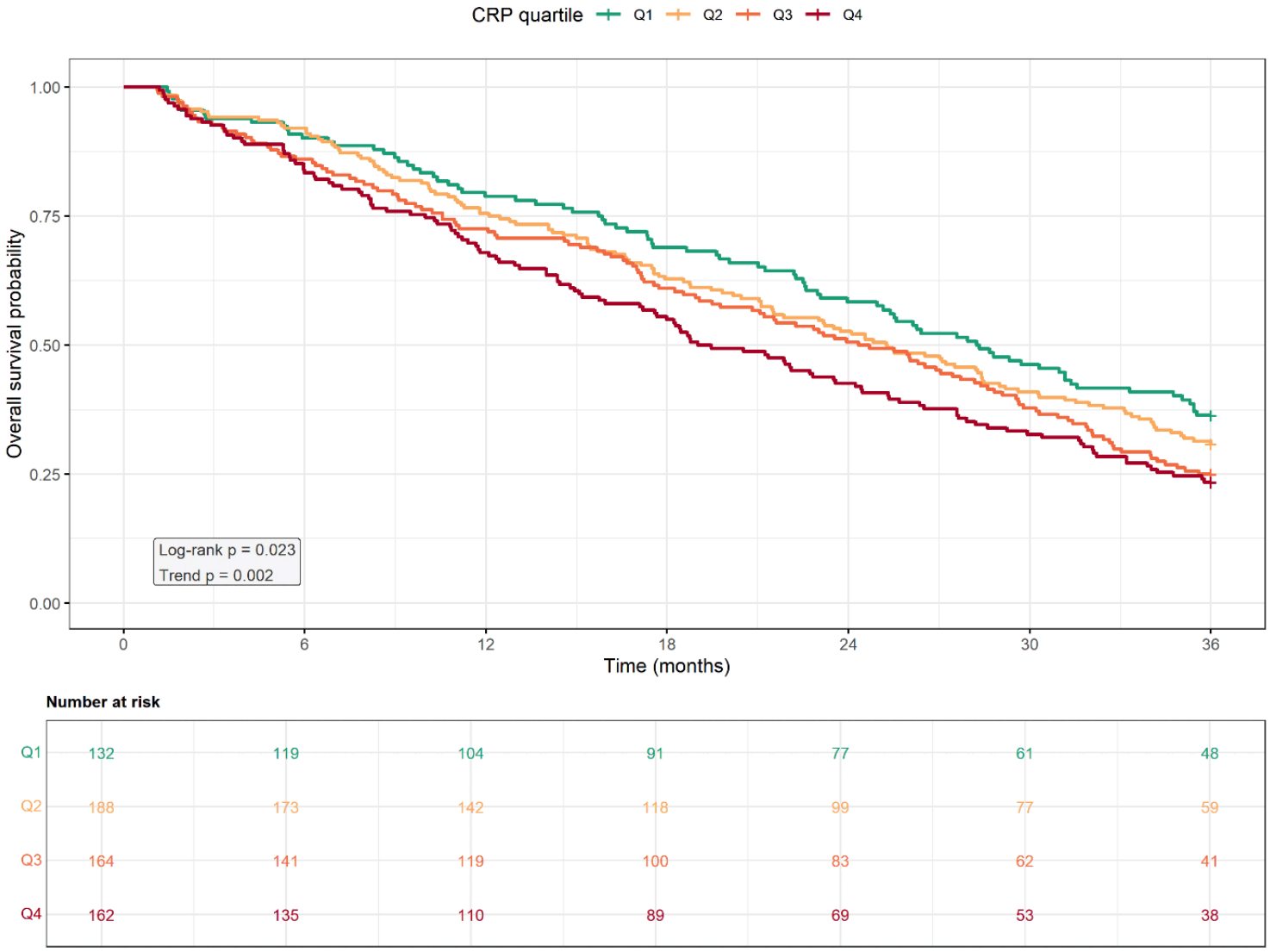


Figure 2

Kaplan–Meier survival according to baseline CRP quartile. Time from the index outpatient visit to all-cause death, stratified by baseline CRP quartile; follow-up was administratively censored at 36 months. Survival decreased progressively across ascending quartiles (log-rank p = 0.023; log-rank test for trend p = 0.002). Numbers at risk are shown beneath the plot. CRP, C-reactive protein.

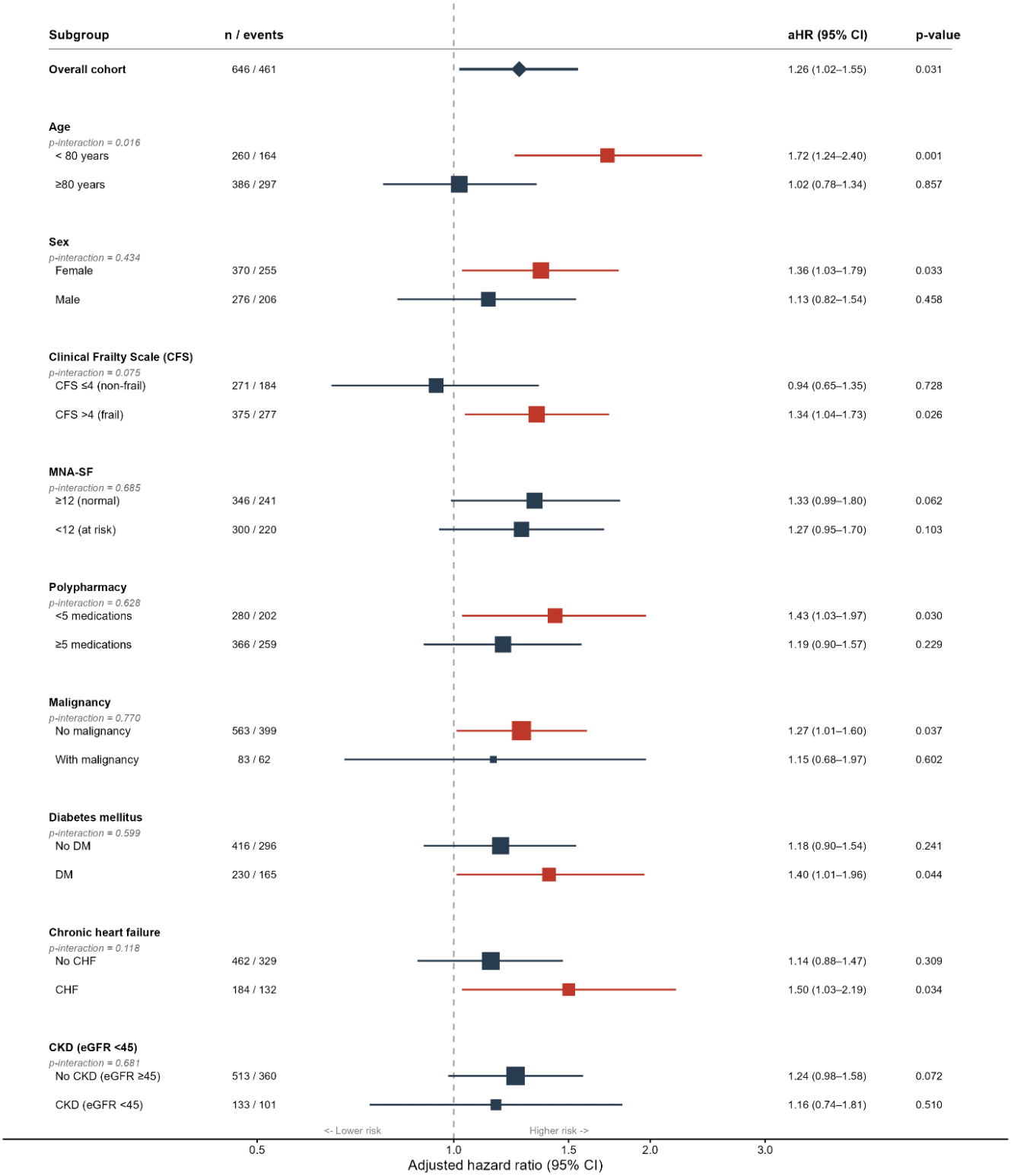


Figure 3

Effect modification of the CRP–time-to-death association across prespecified subgroups (forest plot). Adjusted hazard ratios (95% CI) for baseline CRP ≥10 versus <10 mg/L and time to all-cause death, overall and within prespecified subgroups, from Cox models adjusted for age, sex, Clinical Frailty Scale and Mini Nutritional Assessment–Short Form. The association was significantly modified by age (p for interaction 0.016) and directionally by frailty (p for interaction 0.075). aHR, adjusted hazard ratio; CFS,

Clinical Frailty Scale; CI, confidence interval; CRP, C-reactive protein; MNA-SF, Mini Nutritional Assessment–Short Form.

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