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Two Years with COVID-19: The Electronic Frailty Index Identifies High-Risk Patients in the Stockholm GeroCovid Study

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Keywords
Frailty · COVID-19 · Electronic frailty index · Comorbidity · Older adults

Abstract
Introduction: Frailty, a measure of biological aging, has been linked to worse COVID-19 outcomes. However, as the mortality differs across the COVID-19 waves, it is less clear whether a medical record-based electronic frailty index (eFI) that we have previously developed for older adults could be used for risk stratification in hospitalized COVID-19 patients. ***Objectives:*** The aim of the study was to examine the association of frailty with mortality, readmission, and length of stay in older COVID-19 patients and to compare the predictive accuracy of the eFI to other frailty and comorbidity measures. ***Methods:*** This was a retrospective cohort study using electronic health records (EHRs) from nine geriatric clinics in Stockholm, Sweden, comprising 3,980 COVID-19 patients (mean age 81.6 years) admitted between March 2020 and March 2022. Frailty was assessed using a 48-item eFI developed for Swedish geriatric patients, the Clinical Frailty Scale, and the Hospital Frailty Risk Score. Comorbidity was measured using the Charlson Comorbidity Index. We analyzed in-hospital mortality and 30-day readmission using logistic regression, 30-day and 6-month mortality using Cox regres-

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sion, and the length of stay using linear regression. Predictive accuracy of the logistic regression and Cox models was evaluated by area under the receiver operating characteristic curve (AUC) and Harrell's C-statistic, respectively. ***Results:*** Across the study period, the in-hospital mortality rate decreased from 13.9% in the first wave to 3.6% in the latest (Omicron) wave. Controlling for age and sex, a 10% increment in the eFI was significantly associated with higher risks of in-hospital mortality (odds ratio = 2.95; 95% confidence interval = 2.42–3.62), 30-day mortality (hazard ratio [HR] = 2.39; 2.08–2.74), 6-month mortality (HR = 2.29; 2.04–2.56), and a longer length of stay (β-coefficient = 2.00; 1.65–2.34) but not with 30-day readmission. The association between the eFI and in-hospital mortality remained robust across the waves, even after the vaccination rollout. Among all measures, the eFI had the best discrimination for in-hospital (AUC = 0.780), 30-day (Harrell's C = 0.733), and 6-month mortality (Harrell's C = 0.719). ***Conclusion:*** An eFI based on routinely collected EHRs can be applied in identifying high-risk older COVID-19 patients during the continuing pandemic.

Introduction

While the COVID-19 pandemic has disproportionately affected the older populations [1], it has been argued that frailty and certain comorbidities, rather than chronological age, are the main factors influencing the clinical manifestations and pathophysiological mechanisms of COVID-19 [2]. Frailty, a condition of reduced physiological reserve and heightened vulnerability to stressors [3], is a measure of biological aging that captures the heterogeneity in health during aging [4] and a strong predictor of mortality across different populations [5]. Accumulating evidence has demonstrated the predictive value of frailty, beyond chronological age, for all-cause mortality in COVID-19 patients [6–11]. Some studies have also demonstrated an association of frailty with increased disease severity, admissions to intensive care units, and prolonged hospital stays in COVID-19 patients [12].

Since the beginning of the COVID-19 pandemic in early 2020, several SARS-CoV-2 variants have emerged [13], including the Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and most recently the Omicron (B.1.1.529) variants. By the end of 2021, Omicron has become the dominant variant in Sweden, leading to a new wave of increased COVID-19 infections, hospital admissions, and mortality [14]. Given its burden on the healthcare system, identifying high-risk COVID-19 patients is crucial for resource allocation, guiding decision making, and planning of follow-up care in the ongoing pandemic. However, existing data on frailty and COVID-19 outcomes are primarily based on earlier pandemic waves. Earlier results also suggested a lower predictive accuracy of frailty for mortality in COVID-19 inpatients compared to community-dwelling adults [15]. Considering the constantly evolving pandemic, it is important to investigate whether the association between frailty and the outcomes in hospitalized COVID-19 patients has changed over time, especially during the Omicron wave that is characterized by decreased disease severity and mortality risk [16, 17].

Frailty and its association with COVID-19 outcomes may also differ depending on the choice of frailty assessment tool [8, 11]. The Clinical Frailty Scale (CFS) [18], a clinical judgment-based tool with generally high accuracy, has been widely used during the COVID-19 pandemic due to its easy implementation in many settings [19]. However, the CFS requires in-person evaluation and may be somewhat subjective [20]. It is also not routinely assessed in all hospitals in Sweden. An alternative measure of frailty is the Hospital Frailty Risk Score (HFRS) calculated based on International Classification of Diseases, Tenth Revision (ICD-10) codes [21]; however, only some studies [22], but not others [15, 23, 24], have found an association between the HFRS and COVID-19 mortality in hospitalized patients. The Rockwood frailty index (FI) is one of the best-validated frailty measures [25], but its assessment is resource-intensive and only few studies with relatively small sample sizes have examined its predictive value for COVID-19 mortality [26–28].

Recent advances in utilizing medical health records have fueled the development of electronic frailty indexes (eFIs), i.e., frailty scales that build on the Rockwood FI framework and share its key characteristics [29, 30]. We recently developed such an eFI based on routinely collected electronic health records (EHRs) for geriatric patients in Stockholm, Sweden [31]. We based the Swedish eFI model on the US model by Pajewski et al. [30], as the data contained in the EHRs in the Stockholm region are compatible with the US eFI model. We have previously shown that the Swedish eFI is associated with adverse outcomes in several geriatric patient groups (e.g., fragility fracture, congestive heart failure, dementia), but it is less clear if the eFI has similar utility in COVID-19 patients. Compared to regular geriatric patients who generally have lower and more stable mortality rates over time, COVID-19 patients admitted to geriatric hospitals in Sweden represent a different patient group, who typically have

higher mortality rates, younger age, and longer lengths of stay [32, 33]. The primary aim of this study was to assess the association between the Swedish eFI and adverse outcomes (mortality, readmission, and length of stay) in hospitalized older COVID-19 patients across the pandemic waves. We also compared the predictive accuracy of the Swedish eFI to other validated frailty and comorbidity measures.

Materials and Methods

Study Population

In this retrospective cohort study, we extracted EHRs of 36,221 patients (60,273 admissions) who were admitted to nine geriatric clinics in the Stockholm area between March 1, 2020 and March 21, 2022. These clinics include both standalone geriatric hospitals and ward units situated in larger emergency hospitals, which generally enroll older patients with reduced physical and/or cognitive function, multiple comorbidities, and in need of geriatric medical care and/or rehabilitation. We excluded admissions with (i) missing discharge information (n = 912), (ii) a hospital stay <24 h (n = 2,077), and (iii) insufficient data for calculation of the eFI due to missing functional or laboratory data (n = 16,824). Only patients treated for COVID-19 were included in the present analysis; we have previously analyzed a different population of patients admitted to these clinics [31]. COVID-19 was determined by either a positive result of reverse transcriptase polymerase chain reaction (RT-PCR) or a clinical diagnosis for those with a negative RT-PCR but with typical symptoms and computed tomography scan findings (i.e., ICD-10 codes U07.1 or U07.2). For patients with multiple admissions, only the first admission with a COVID-19 diagnosis was included, yielding a final sample size of 3,980 COVID-19 patients. This study was approved by the Swedish Ethical Review Authority.

Given the large fluctuation of COVID-19 infection and mortality rates during the pandemic in Sweden, we considered five study periods (waves) according to the data on confirmed COVID-19 cases and vaccination coverage by the Public Health Agency of Sweden (2022). Period 1 ("1st wave") was defined from March 1 to August 31, 2020; period 2 ("2nd wave") from September 1, 2020, to January 31, 2021; period 3 ("3rd wave") from February 1 to April 20, 2021; period 4 from April 21 to December 31, 2021; and period 5 ("the Omicron wave") from January 1 to March 21, 2022. The start of the period 4 (April 21, 2021) also marks the date when most individuals in our target population have received two vaccination doses, whereas the start of the period 5 (January 1, 2022) marks the date when most individuals in our target population have received three vaccination doses [14]. The number of admitted COVID-19 patients and mortality rates throughout the five study periods are illustrated in online supplementary Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000527206).

Assessment of Frailty and Comorbidity

Three frailty measures (eFI, CFS, HFRS) and a comorbidity measure (Charlson Comorbidity Index [CCI]) were used:

- A Swedish eFI was derived based on a US model by Pajewski et al. [30]. Details on its development and coding of the eFI items have been previously described [31]. Briefly, a list of 48 items from disease diagnoses (29 items), functional abilities, and other health indicators such as oral health, falls, and weight loss (10 items), and laboratory measures (9 items) were included (online suppl. Table 1). Following the principles of the deficit accumulation model [25], the eFI was calculated as a proportion of deficits out of the total number of non-missing items (e.g., a patient having 6 deficit points out of 42 non-missing items would have an eFI of 6/42 = 0.14). To ensure multidimensionality of the eFI along the Rockwood FI framework, those with <30 available eFI items or those missing more than half of the functioning and/or laboratory deficits were excluded from the analysis. Patients were categorized into four eFI groups analogously as described by Clegg et al. [29]: fit (≤0.15), mild frailty (>0.15–0.2), moderate frailty (>0.2–0.25), and severe frailty (>0.25).
- The CFS was scored and recorded in EHRs by a trained nurse or physician during admission, based on the patients' physical functioning, comorbidity, and cognition. It is an ordinal scale ranging from 1 ("very fit") to 9 ("terminally ill"). Following previous work [6], we categorized patients into three CFS groups: 1–3 (low risk), 4–5 (moderate risk), and 6–9 (high risk).
- The HFRS was calculated based on 109 frailty-associated ICD-10 codes, using the algorithm described by Gilbert et al. [21]. Patients were grouped into low (<5), intermediate (5–15), and high (>15) risk of frailty.
- The CCI was computed as a weighted score of 19 comorbidities defined using ICD-10 codes. An algorithm adapted for Swedish settings was used [34]. It was considered as a continuous variable in the analysis.

Outcomes

Study outcomes included (i) in-hospital mortality, (ii) 30-day mortality, (iii) 6-month mortality, (iv) 30-day readmission to any of the nine geriatric clinics included in this study, and (v) the length of hospital stay. Dates of death were obtained from the Swedish Population Register. 30-day and 6-month mortality were calculated from the date of admission to the date of death; those who were alive at the end of the study were censored on March 21, 2022. Only individuals discharged home after the first admission were included in the 30-day readmission analysis (n = 2,599).

Statistical Analysis

Summary statistics across the five study periods were compared using analysis of variance or Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality and 30-day readmission using logistic regression models. Cox proportional-hazards models were used to estimate hazard ratios for 30-day and 6-month mortality. The length of stay was assessed using linear regression models. All the models were adjusted for age and sex (model 1). Further, we performed generalized estimating equations or stratified Cox models to account for the clustering of patients in the geriatric clinics (model 2).

In a subgroup of patients with non-missing data on all the frailty and comorbidity measures (n = 1,963), we evaluated the predictive accuracy (discrimination) of the eFI, in comparison to other frailty and comorbidity measures, for in-hospital mortality using the area under the receiver operating characteristic curve (AUC), and for 30-day and 6-month mortality using the Harrell's C-statis-

Table 1. Characteristics of COVID-19 patients by the period of first hospital admission

Characteristic	Overall	Period 1 Mar 1, 2020 to Aug 31, 2020	Period 2 Sep 1, 2020 to Jan 31, 2021	Period 3 Feb 1, 2021 to Apr 20, 2021	Period 4 Apr 21, 2021 to Dec 31, 2021	Period 5 Jan 1, 2022 to Mar 21, 2022	p[a]
No. of patients, *n* (%)	3,980 (100)	1,152 (28.9)	1,161 (29.2)	586 (14.7)	405 (10.2)	676 (17.0)	
Age, mean ± SD, year	81.6±8.5	82.2±8.6	82.4±7.9	79.0±8.1	79.7±9.4	82.4±8.4	<0.001
Age category, *n* (%)							
<65 years	104 (2.6)	25 (2.2)	18 (1.6)	19 (3.2)	24 (5.9)	18 (2.7)	<0.001
65–74 years	718 (18.0)	205 (17.8)	180 (15.5)	144 (24.6)	96 (23.7)	93 (13.8)	
75–84 years	1,608 (40.4)	434 (37.7)	473 (40.7)	277 (47.3)	145 (35.8)	279 (41.3)	
85–94 years	1,336 (33.6)	415 (36.0)	434 (37.4)	125 (21.3)	123 (30.4)	239 (35.4)	
≥95 years	214 (5.4)	73 (6.3)	56 (4.8)	21 (3.6)	17 (4.2)	47 (7.0)	
Men, *n* (%)	1,837 (46.2)	525 (45.6)	524 (45.1)	286 (48.8)	194 (47.9)	308 (45.6)	0.58
eFI, median (IQR)	0.179 (0.139–0.221)	0.188 (0.148–0.232)	0.181 (0.142–0.221)	0.163 (0.118–0.203)	0.171 (0.129–0.215)	0.182 (0.143–0.225)	<0.001
eFI category, *n* (%)							
Fit (≤0.15)	1,228 (30.9)	306 (26.6)	343 (29.5)	248 (42.3)	139 (34.3)	192 (28.4)	<0.001
Mild frailty (>0.15–0.2)	1,301 (32.7)	367 (31.9)	383 (33.0)	184 (31.4)	139 (34.3)	228 (33.7)	
Moderate frailty (>0.2–0.25)	937 (23.5)	305 (26.5)	291 (25.1)	116 (19.8)	70 (17.3)	155 (22.9)	
Severe frailty (>0.25)	514 (12.9)	174 (15.1)	144 (12.4)	38 (6.5)	57 (14.1)	101 (14.9)	
CFS score, median (IQR)	5 (4–6)	6 (4–7)	5 (4–6)	4 (3–6)	5 (4–6)	6 (4–7)	<0.001
CFS category, *n* (%)							
1–3	350 (8.8)	57 (4.9)	118 (10.2)	94 (16.0)	44 (10.9)	37 (5.5)	<0.001
4–5	702 (17.6)	173 (15.0)	229 (19.7)	112 (19.1)	66 (16.3)	122 (18.0)	
6–9	911 (22.9)	296 (25.7)	298 (25.7)	88 (15.0)	65 (16.0)	164 (24.3)	
Missing	2,017 (50.7)	626 (54.3)	516 (44.4)	292 (49.8)	230 (56.8)	353 (52.2)	
HFRS, median (IQR)	2.2 (0.5–4.4)	2.7 (1.2–4.7)	2.2 (0.6–4.4)	1.5 (0–3.8)	1.6 (0–3.7)	2.3 (1–4.8)	<0.001
HFRS category, *n* (%)							
Low risk (<5)	3,129 (78.6)	876 (76.0)	915 (78.8)	485 (82.8)	342 (84.4)	511 (75.6)	<0.001
Intermediate risk (5–15)	840 (21.1)	268 (23.3)	245 (21.1)	101 (17.2)	62 (15.3)	164 (24.3)	
High risk (>15)	11 (0.3)	8 (0.7)	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.1)	
CCI, mean ± SD	1.42±1.52	1.60±1.62	1.35±1.45	1.13±1.35	1.33±1.50	1.53±1.58	<0.001
In-hospital mortality, *n* (%)	333 (8.4)	160 (13.9)	100 (8.6)	27 (4.6)	22 (5.4)	24 (3.6)	<0.001
Discharged to home, *n* (%)	2,599 (65.3)	727 (63.2)	710 (61.2)	418 (71.3)	289 (71.4)	455 (67.4)	<0.001
30-day readmission,[b] *n* (%)	243 (9.3)	92 (12.7)	56 (7.9)	35 (8.4)	16 (5.5)	44 (9.7)	0.002
Length of stay, median (IQR), day	8.61 (5.88–13.01)	9.05 (6.36–14.36)	9.06 (5.99–13.92)	7.86 (4.96–12.38)	7.91 (5.88–12.72)	7.53 (5.74–10.93)	<0.001

CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale; eFI, electronic frailty index; HFRS, Hospital Frailty Risk Score; IQR, interquartile range; SD, standard deviation. [a] p values for comparison between periods, based on ANOVA or Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. [b] Only patients discharged to home after the first admission were included for analysis of 30-day readmission.

tics. The 95% CIs for the Harrell's C-statistics were calculated using 1,000 bootstrapping resampling.

We performed subgroup analysis for the association between the eFI and in-hospital mortality by (i) the five study periods to account for variations during the pandemic, (ii) age groups and sex to assess if the association differed in younger versus older populations and in women versus men, and (iii) admitting clinics to test whether the eFI may predict mortality in the different clinics. R version 4.0.5 was used for all analyses.

Results

Of the included 3,980 geriatric COVID-19 patients, 53.8% were women, and the mean age was 81.6 years (Table 1). The overall in-hospital mortality rate was 8.4%, and the average length of stay was 8.6 days. The median eFI was 0.179 (IQR: 0.139–0.221; range: 0–0.404); the proportions of fit, mild frailty, moderate frailty, and severe frailty in the sample were 30.9%, 32.7%, 23.5%, and 12.9%, respectively. The eFI was moderately correlated with other measures, Spearman's correlations of which were 0.473 with the CFS, 0.345 with the HFRS, and 0.391 with the CCI.

Across the study periods between March 2020 and March 2022, there was a higher number of COVID-19 patients admitted to the nine geriatric clinics during periods of high community transmission, especially during the first two pandemic waves in 2020 before the vaccination rollout (periods 1 & 2) and the Omicron wave in early 2022 (period 5) (online suppl. Fig. 1). Patients admitted during periods 1, 2, and 5 (mean age ~82 years) appeared to be older than those admitted during periods 3 and 4 (i.e., 3rd wave and vaccination rollout in 2021; mean age ~79 years) ($p < 0.001$), and they also tended to

Table 2. Associations of frailty and comorbidity measures with mortality outcomes

Model	In-hospital mortality, OR (95% CI)		30-day mortality, HR (95% CI)		6-month mortality, HR (95% CI)	
	model 1[a]	model 2[b]	model 1[a]	model 2[b]	model 1[a]	model 2[b]
eFI						
Continuous, per 0.1 increase	2.95 (2.42–3.62)*	2.87 (2.46–3.36)*	2.39 (2.08–2.74)*	2.30 (2.01–2.64)*	2.29 (2.04–2.56)*	2.28 (2.03–2.56)*
Categorical						
Fit (≤0.15)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Mild frailty (>0.15–0.2)	1.73 (1.15–2.64)*	1.81 (1.54–2.14)*	1.56 (1.17–2.08)*	1.60 (1.20–2.13)*	1.48 (1.18–1.85)*	1.53 (1.22–1.91)*
Moderate frailty (>0.2–0.25)	3.41 (2.31–5.15)*	3.60 (2.71–4.79)*	3.02 (2.30–3.97)*	3.10 (2.35–4.09)*	2.69 (2.17–3.34)*	2.81 (2.26–3.50)*
Severe frailty (>0.25)	6.71 (4.52–10.2)*	6.55 (5.46–7.86)*	4.70 (3.54–6.23)*	4.51 (3.38–6.01)*	4.20 (3.35–5.26)*	4.20 (3.34–5.29)*
CFS[c]						
Continuous, per point increase	1.55 (1.37–1.77)*	1.71 (1.48–1.96)*	1.36 (1.24–1.48)*	1.43 (1.31–1.57)*	1.37 (1.27–1.48)*	1.45 (1.35–1.57)*
Categorical						
1–3	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
4–5	1.48 (0.75–3.19)	1.55 (0.74–3.29)	1.33 (0.83–2.11)	1.42 (0.89–2.26)	1.56 (1.04–2.33)*	1.65 (1.10–2.47)*
6–9	4.06 (2.18–8.44)*	4.92 (3.14–7.73)*	2.57 (1.66–3.96)*	2.96 (1.91–4.60)*	2.94 (2.01–4.30)*	3.41 (2.32–5.01)*
HFRS						
Continuous, per point increase	1.09 (1.05–1.13)*	1.08 (1.03–1.12)*	1.07 (1.04–1.09)*	1.06 (1.03–1.08)*	1.07 (1.05–1.09)*	1.06 (1.04–1.08)*
Categorical						
Low risk (<5)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Intermediate risk (5–15)	1.76 (1.37–2.25)*	1.65 (1.24–2.18)*	1.47 (1.22–1.76)*	1.41 (1.17–1.69)*	1.50 (1.29–1.74)*	1.44 (1.23–1.67)*
High risk (>15)	No observation	No observation	No observation	No observation	1.08 (0.35–3.38)	1.05 (0.34–3.28)
CCI						
Continuous, per point increase	1.22 (1.14–1.30)*	1.20 (1.13–1.28)*	1.19 (1.14–1.25)*	1.18 (1.13–1.23)*	1.25 (1.20–1.29)*	1.24 (1.19–1.28)*

CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale; CI, confidence interval; eFI, electronic frailty index; HFRS, Hospital Frailty Risk Score; HR, hazard ratio; OR, odds ratio. * $p < 0.05$. [a] Model 1 was adjusted for age and sex. ORs for in-hospital mortality were estimated by logistic regression models, and HRs for 30-day and 6-month mortality were estimated by Cox models. [b] Model 2 was adjusted for age and sex, and additionally accounted for clustering of patients in the nine geriatric clinics. ORs for in-hospital mortality were estimated by generalized estimating equation with the logit link, and HRs for 30-day and 6-month mortality were estimated by stratified Cox regression models. [c] Sample size was smaller in analysis of CFS (n = 1,963) due to missing data.

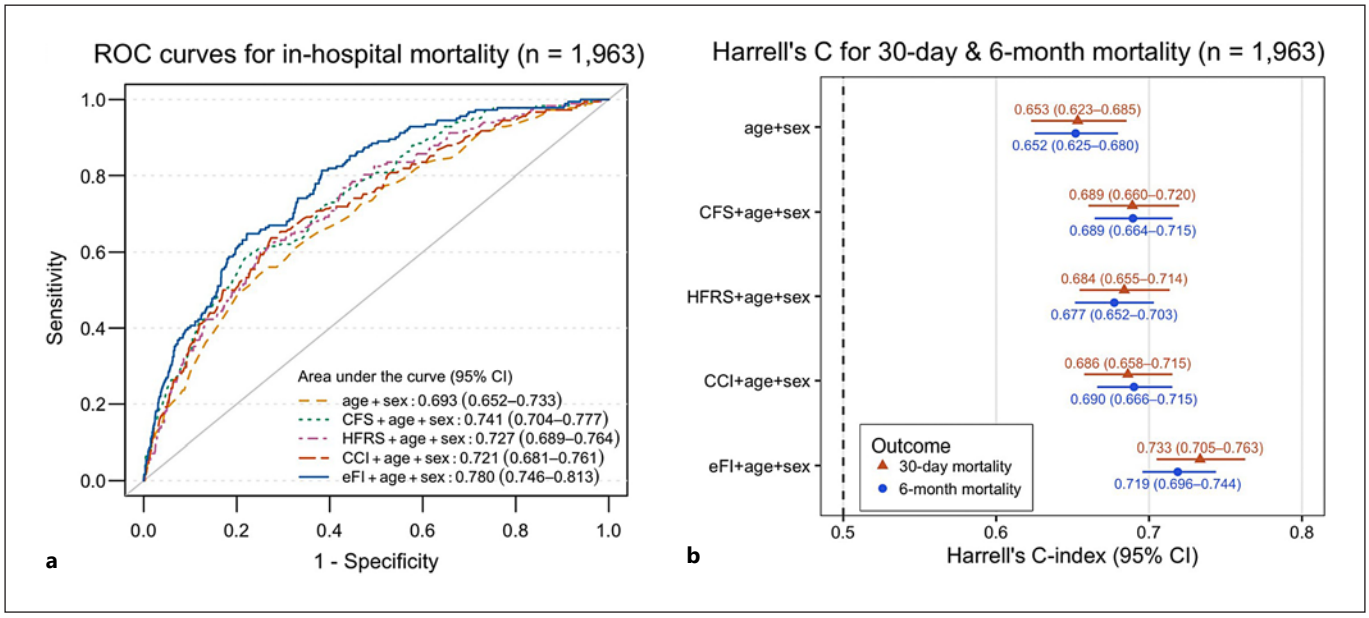

Fig. 1. Predictive accuracies of frailty and comorbidity measures for mortality outcomes in the subgroup of patients with all measures available (n = 1,963). **a** Area under the receiver operating characteristics curves for in-hospital mortality. (**b**) Harrell's C-statistics from Cox models for 30-day and 6-month mortality. CFS, HFRS, CCI, and eFI were considered as continuous variables in all the models. CFS, Clinical Frailty Scale; HFRS, Hospital Frailty Risk Score; CCI, Charlson Comorbidity Index; eFI, electronic frailty index.

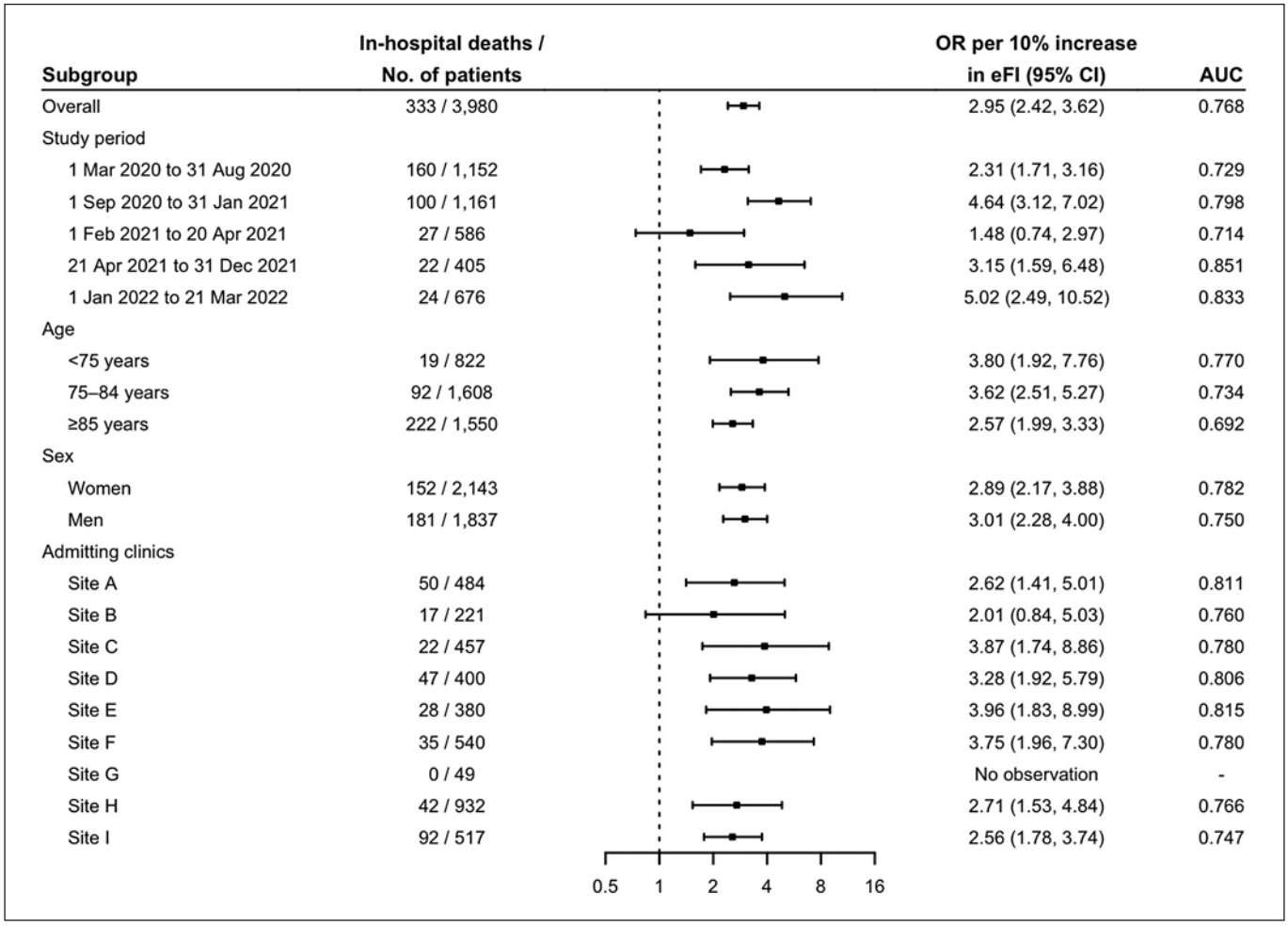

Fig. 2. Subgroup analysis for the association between the electronic frailty index (eFI) and in-hospital mortality, stratified by study period, age, sex, and admitting clinics. ORs and AUCs were calculated from multivariable logistic regression models, where the eFI, age (continuous), and sex were included as independent variables. AUC, area under the receiver operating characteristic curve; CI, confidence interval; OR, odds ratio.

be more frail and multimorbid, as indicated by higher eFI, CFS, HFRS, and CCI scores (Table 1). The mortality rate generally decreased with time, from 13.9% in the 1st wave (March to August 2020) to 3.6% in the Omicron wave (January to March 2022) (online suppl. Fig. 1; Table 1).

Table 2 shows the associations of the frailty and comorbidity measures with the mortality outcomes. The eFI (OR per 10% increase: 2.95, 95% CI: 2.42–3.62), as well as the CFS, HFRS, and CCI, were significantly associated with in-hospital mortality after adjusting for age and sex (model 1). Results were largely consistent when additionally accounting for the admitting clinics (model 2). Among all the frailty and comorbidity measures, adding the eFI to a model with age and sex yielded the greatest AUC of 0.780, suggesting that the eFI had the greatest predictive accuracy for in-hospital mortality (Fig. 1a). In the subgroup analysis (Fig. 2), we observed a significant association between the eFI and in-hospital mortality across all the study periods except period 3 (i.e., 3rd wave); the AUCs were also higher in more recent than earlier periods. Besides, the association tended to be stronger in younger than older age groups (p value for an interaction term between continuous age and eFI = 0.017) but was similar in men and women. The eFI also predicted in-hospital mortality across the nine clinics (AUCs: 0.747–0.815).

We followed the patients up to 6 months from admission and observed higher mortality rates among those in

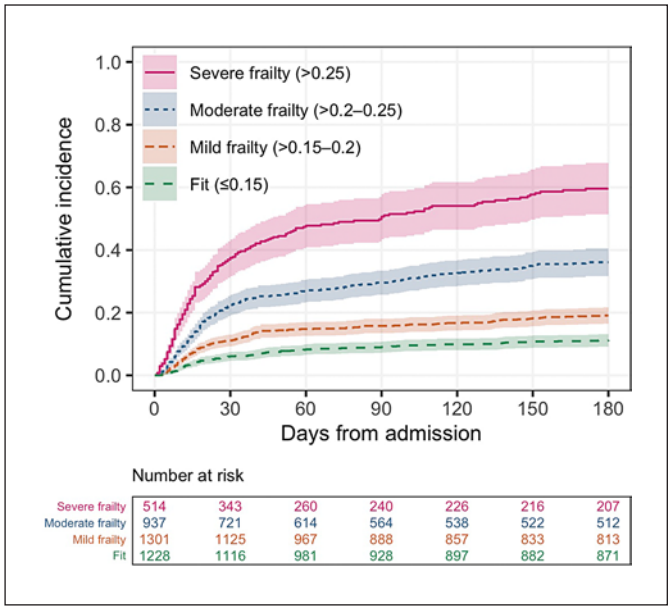

Fig. 3. Cumulative incidence for all-cause mortality over 6 months by categories of the electronic frailty index (eFI).

the higher eFI categories (Fig. 3). The eFI was associated with higher risks of 30-day and 6-month mortality, the age- and sex-adjusted hazard ratios per a 10% increase being 2.39 (95% CI: 2.08–2.74) and 2.29 (95% CI: 2.04–2.56), respectively (Table 2). The eFI, compared to the CFS, HFRS, and CCI, had the greatest predictive accuracy for 30-day (Harrell's C = 0.733) and 6-month mortality (Harrell's C = 0.719) (Fig. 1b). Furthermore, a 10% increase in the eFI was associated with a 2-day longer length of stay (95% CI: 1.65–2.34). Nevertheless, only the CFS (OR per point increase: 1.22; 95% CI: 1.07–1.39), but not the eFI, HFRS, nor CCI, was significantly associated with 30-day readmission (online suppl. Table 2).

Discussion

In this sample of older COVID-19 patients admitted to nine geriatric clinics in Stockholm, Sweden between March 2020 and March 2022, frailty was significantly associated with an increased risk of mortality and a longer length of stay. Despite the overall decrease in the mortality rate over the pandemic waves, the association between the eFI and in-hospital mortality remained robust even after the vaccination rollout in 2021 and during the Omicron wave in early 2022. Moreover, the EHR-based eFI had the best discrimination for short- and long-term mortality compared to the CFS, HFRS, and CCI. Together, these results give support to the utility of the eFI for risk assessment and planning of care in hospitalized COVID-19 patients.

With the complex interactions between new variants, vaccination, and national restrictions, the COVID-19 infection and mortality rates have fluctuated throughout the pandemic [13]. There was a surge in admissions to the included clinics during the Omicron wave, yet we noticed a significantly lower mortality rate in that period compared to previous waves, which is consistent with recent studies suggesting a decreased disease severity of the Omicron variant [16, 17]. Interestingly, patients admitted during the 1st, 2nd, and Omicron waves were older and frailer than those admitted during the 3rd wave in 2021, which may in part be explained by the more stringent selection of admissions during periods of high community spread of COVID-19, leading to a sicker, older, and frailer patient group [33].

Although many studies have found an association between frailty and COVID-19 mortality [6–11], some findings have suggested a relatively lower predictive ability of frailty for mortality in hospitalized COVID-19 patients during earlier pandemic waves, compared to community populations [15, 35]. It is also less known whether the varying patient characteristics and mortality rates have affected the associations over time. Adding to the literature, we demonstrated that frailty was associated with mortality in older COVID-19 patients throughout the 2-year study period. The discriminatory ability of the eFI for in-hospital mortality also appeared to be stronger (AUC > 0.8) in periods 4 and 5, i.e., after most of the patients were fully vaccinated. The increased risk of COVID-19 mortality in frail older adults has been linked to immunosenescence (i.e., gradual decline in immune system with age) and inflammaging (i.e., age-associated chronic, low-grade inflammation) that lead to a weaker immune response to infections and an increased COVID-19 severity [2, 19]. Similarly, the reduced immunogenicity in frail patients may have resulted in decreased effectiveness and an increased risk of adverse events of vaccines [36, 37]. We speculate that after the mass vaccinations in early 2021, only the younger and healthier individuals, but not the frail older adults, have acquired enough immunity to COVID-19, thus explaining the seemingly improved predictive ability of frailty for COVID-19-related mortality in the later periods. Notably, there have been mixed results on whether age and frailty are associated with COVID-19 vaccine immunogenicity among long-term care facilities residents [38–40]. More

studies on the relationships between frailty and COVID-19 immunity are needed to confirm our findings. Moreover, in line with our previous study [15], we found stronger associations between frailty and in-hospital mortality in younger (aged <75) than in the oldest patients (aged ≥85), indicating a greater relative risk conferred by frailty at younger ages. This suggests that the effect of frailty on COVID-19 outcomes is not restricted to the oldest individuals; rather, frailty should be considered as a risk factor in younger patients too.

Without a "gold standard," various frailty assessment tools have been used in the literature depending on the study setting and data availability. Previous studies in COVID-19 patients mostly used the CFS [6–11], which is a simple, efficient, and accurate clinical tool [18]. Nevertheless, it requires in-person assessment and may not always be available, e.g., the CFS was missing in ~50% of patients in our sample due to variations in data collection practice in different hospitals [31]. Some studies used the HFRS, but only weak association with COVID-19 mortality was found [15, 23, 24]. In contrast, the association between the CFS and COVID-19 mortality seems robust [7]. This may be explained by the slightly dissimilar concepts captured: the CFS focuses mainly on functioning and disability [18], while the diagnosis code-based HFRS is more similar to a comorbidity measure [21]. We constructed the eFI based on the deficit accumulation model [25, 29], including comorbidities, disabilities, cognition, and laboratory deficits, adhering to the multidimensional definition of frailty. The eFI had moderate correlations with the CFS, HFRS, and CCI, and had good discrimination for in-hospital mortality, suggesting that the multidimensional construct of frailty may predict COVID-19 mortality better than mere disability and multimorbidity.

Few studies have investigated outcomes other than in-hospital mortality in COVID-19 patients [8]. Contributing to the evidence base, we found that frailty tools, especially the eFI, were associated with higher risks of 30-day mortality, 6-month mortality, and a longer length of stay. However, most of the frailty and comorbidity measures did not show a significant association with 30-day readmission, which may partly be due to misclassification of patients who were readmitted to other hospitals than the nine included geriatric clinics. This matter warrants further studies in samples with higher readmission coverage.

This study included a relatively large sample of COVID-19 patients admitted to nine geriatric clinics in the Stockholm region between 2020 and 2022, allowing us to examine the relationship between frailty and outcomes in COVID-19 patients across different periods during the pandemic. Our current results further strengthen the clinical utility of the eFI such that COVID-19 patients presenting with higher eFI scores can be provided with more comprehensive care and closer monitoring during and after hospitalization. We have previously observed that the Swedish eFI has good predictive accuracy for adverse outcomes also in geriatric patients treated for other diagnoses than COVID-19 [31]. However, our findings may not be generalizable to all COVID-19 patients, such as those treated in intensive care units. Due to a lack of data, we were also unable to account for several other risk factors (e.g., socioeconomic status, smoking), SARS-CoV-2 variants, and COVID-19 vaccination. Nevertheless, most older adults in Stockholm were most likely vaccinated with two doses (i.e., first vaccination and a booster dose) after April 21, 2021 [14], and we showed that the eFI was associated with in-hospital mortality also after this date.

In summary, to the best of our knowledge, this is the first study that used an eFI based on routinely collected EHRs to identify high-risk COVID-19 patients. The eFI was associated with in-hospital mortality throughout the pandemic, and it outperformed other frailty and comorbidity measures, including the CFS, HFRS, and CCI, in discriminating short- and long-term mortality. During the continuing global spread of COVID-19, the eFI, when automated, could be a useful and efficient tool for risk stratification in hospitalized patients with COVID-19.

Preprint

A preprint version of this article is available on medRxiv [41].

Statement of Ethics

The Swedish Ethical Review Authority approved the study (Dnr 2020-02146, 2020-03345, 2021-00595, and 2021-02096). As a retrospective analysis of de-identified data, written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dorota Religa, Juulia Jylhävä, Sara Hägg, Maria Eriksdotter, and Tommy Cederholm contributed to the study concept and design; Jonathan K. L. Mak, Ralf Kuja-Halkola, and Laura Kananen performed data analyses; Jonathan K.L. Mak and Juulia Jylhävä drafted the manuscript; Maria Eriksdotter, Martin Annetorp, Anne-Marie Boström, Miia Kivipelto, Carina Metzner, Viktoria Bäck Jerlardtz, Malin Engström, Peter Johnson, Lars Göran Lundberg, Elisabet Åkesson, Carina Sühl Öberg, Maria Olsson, Tommy Cederholm, and Dorota Religa contributed to data acquisition. All the authors contributed to interpretation of the results and participated in writing and reviewing of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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