



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

The role of Frailty on Adverse Outcomes Among Older Patients with COVID-19



Harun Kundi, MD, MMSc^{a,1,*}, Elif Hande Özcan Çetin, MD^a, Uğur Canpolat, MD^b,
Sevgi Aras, MD^c, Osman Celik, MD^d, Naim Ata, MD^d, Suayip Birinci, MD^d,
Serkan Çay, MD^e, Özcan Özeke, MD^e, Ibrahim Halil Tanboğa, MD, PhD^{f,g},
Serkan Topaloğlu, MD^e

^a Ankara City Hospital, Department of Cardiology, Ankara, Turkey

^b Hacettepe University, Department of Cardiology, Ankara, Turkey

^c Ankara University, Department of Geriatric Medicine, Ankara, Turkey

^d Republic of Turkey Ministry of Health, Ankara, Turkey

^e University of Health Sciences, Ankara City Hospital, Department of Cardiology, Ankara, Turkey

^f Nişantaşı University, Hisar Intercontinental Hospital, Cardiology, Istanbul, Turkey

^g Ataturk University Biostatistics, Erzurum, Turkey

ARTICLE INFO

Article history:

Accepted 24 September 2020

Available online 28 September 2020

Keywords:

COVID-19

Frailty

SUMMARY

Background: Diagnosis and screening of frailty, a condition characterized by an increased vulnerability to adverse outcomes of COVID-19, has emerged as an essential clinical tool which is strongly recommended by healthcare providers concerned with hospitalized elderly population. The data showing the role of frailty in patients infected with COVID-19 is needed.

Methods: This was a nationwide cohort study conducted at all hospitals in Turkey. All COVID-19 hospitalized patients (≥ 65 years) were included. Patients who were alive and not discharged up to July 20, 2020, were excluded. The frailty was assessed by using the "Hospital Frailty Risk Score" (HFRS). Patients were classified into three risk groups of frailty based on previously validated cut points as low (<5 points), intermediate (5–15 points), and high (>15 points). Additionally, patients who had the HFRS of ≥ 5 were defined as frail. The primary outcome was in-hospital mortality rates by frailty group.

Results: Between March 11, 2020, and June 22, 2020, a total of 18,234 COVID-19 patients from all of 81 provinces of Turkey were included. Totally, 12,295 (67.4%) patients were defined as frail (HFRS of >5) of which 2,801 (15.4%) patients were categorized in the highest level of frailty (HFRS of >15). Observed in-hospital mortality rates were 697 (12.0%), 1,751 (18.2%) and 867 (31.0%) in low, intermediate and high hospital frailty risk, respectively ($p < 0.001$). Compared with low HFRS (<5), the adjusted odds ratios for in-hospital mortality were 1.482 (1.334–1.646) for intermediate HFRS (5–15) and 2.084; 95% CI, 1.799–2.413 for high HFRS (>15).

Conclusions: As a claims-based frailty model, the HFRS provides clinicians and health systems, a standardized tool for an effective detection and grading of frailty in patients in COVID-19. A frailty-based tailored management of the older population may provide a more accurate risk categorization for both therapeutic and preventive strategies.

© 2020 The British Infection Association. Published by Elsevier Ltd. All rights reserved.

* Corresponding author: Harun Kundi, MD, MMSc, Ankara City Hospital, Department of Cardiology, Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya/ANKARA, Turkey.

E-mail address: harunkundi@hotmail.com (H. Kundi).

¹ Tweeter: @HarunKundi

Introduction

The novel severe acute respiratory syndrome coronavirus-2 disease (COVID-19) pandemic has brought an enormous burden to current healthcare systems worldwide with poor outcomes especially among older people.¹ However, other comorbidities besides age were shown to affect the prognostic risk, suggesting that we need a more comprehensive approach.² The assessment and adaptation of frailty using appropriate tools in clinical practice to de-

termine health outcomes should constitute the cornerstone of patient management.³ Thus, the notion of frailty as a determinant of an increased vulnerability comes back to the center of the debate, especially for its eligibility as a predictor of adverse outcomes in older patients with COVID-19.^{4,5} Although frailty has shown to be a reliable predictor of clinical and healthcare-related outcomes in various conditions,^{6,7} the outcomes of frail older patients diagnosed with COVID-19 remain unclear and arguable.^{8–13}

In the current study, we aimed to assess the prevalence of frailty, the predictive value of frailty for adverse outcomes if any, and lastly, the value of adding frailty to the contemporary comorbidity-based risk adjustment tools in our nationwide COVID-19 patients.

Material and Methods

Study Cohort

All hospitalized patients aged ≥ 65 years old with at least one positive reverse transcriptase-polymerase chain reaction (RT-PCR) test for COVID-19 between March 11, 2020, and June 22, 2020, were planned to be included in the study. For patients with recurrent hospitalizations, the index admission was included in the analyses. Patients with missing dates of admission or discharge were excluded. Baseline comorbidities were identified using codes from the International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) (**Supplemental Table 1**). All covariates were ascertained using ICD-10-CM codes from 2-years before the date of index admission for COVID-19. All these data were obtained from two different national digital health record systems, including the “Public Health Management System module” (PHMS) to collect COVID-19 specific data and the “e-Pulse” system to obtain ICD-10-CM codes in the last two years which were explained in detail below. The Turkish Ministry of Health approved the study with a waiver of informed consent for retrospective data analysis.

National Data Collection

Since the year 2014, the Ministry of Health has set up health data warehouses covering the whole country and plans to use informatics applications through data obtained from the center. In 2015, the Ministry of Health established the “e-Pulse” system as a national health information system, which can be accessed only by authorized persons and institutions, which has a broad bandwidth and covers the whole country.¹⁴ Since Turkey operates a mandatory universal system called General Healthcare Insurance (GHI), all Turkish residents can receive medical services free of charge by the Social Security Institution (SSI).

All study data were recalled from the abovementioned centralized national database, which was controlled by the Turkish Ministry of Health. Ministry of Health presents services using Big Data technology, and these systems are also integrated into each other: e-Pulse and National Healthcare Information System (NHIS). These services enable officers and individuals to reach and use health records, make appointments with the hospitals and doctors, and track their reports. On January 22, 2020, COVID-19 Scientific Advisory Board for the Turkish Ministry of Health was set up, and COVID-19 dedicated PHMS was created as a real-time centralized national health registry system for all healthcare providers for outbreak surveillance during COVID-19 era.¹⁵ The inclusion of a case tracking module into the PHMS allowed a constant monitoring of all the possible COVID-19 cases, of people who came from abroad and need isolation at home, and of people who came into contact with COVID-19 cases. The monitoring process included all the phases from the COVID-19 detection to the hospitalization.¹⁵ As of

March 17, 2020, the data has been entered retrospectively to enable access to the old data through module.¹⁵

Assessment of Frailty

The frailty was assessed by using the “Hospital Frailty Risk Score” (HFRS), which was previously developed and validated in an older British cohort.¹⁶ The calculation of HFRS was based on one or more of 109 ICD-10-CM diagnosis codes (**Supplemental Table 2**) recalled from all diagnosis codes of any hospitalization within the last two years. According to calculated HFRS, patients were classified into three frailty risk groups based on previously validated cut points as low (< 5 points), intermediate (5–15 points), and high (> 15 points).¹⁶ Additionally, patients who had the HFRS of ≥ 5 were defined as frail.¹⁶

Study Outcomes

The primary outcome of the study was in-hospital all-cause mortality. The secondary outcomes of the study were a long length of hospital stay (long-LOS) defined as hospitalization for more than ten days, the requirement for the intensive care unit (ICU), and mechanical ventilation (MV). To ensure consistent ascertainment that all outcomes were correctly identified, patients who were not discharged up to July 20, 2020, were excluded.

Statistical Analysis

Continuous and categorical variables are presented as mean (SD) and count (percentage), respectively. We used independent t-test for continuous variables to analyze the difference between survivors and non-survivors. We compared primary and secondary outcomes among frailty risk categories defined as low-risk, intermediate-risk, and high-risk using analysis of variance tests as appropriate. Multivariable logistic regression models after adjustment for age, sex, and comorbidities were constructed to assess the independent association of frailty risk categories with study outcomes. Additionally, in sensitivity analyses, HFRS (as a continuous variable) was used to evaluate the association of frailty with study outcomes.

As a sensitivity analysis, restricted cubic spline curves with five knots were used to show the non-linear associations of HFRS with outcomes. For each outcome, Harrell’s concordance statistics (c-statistics) were used to assess model discrimination, and the improvement in discrimination with the addition of the frailty risk categories was evaluated by the change in the c-statistic and the DeLong test.^{17,18} An integrated discrimination improvement (IDI) metric was also used to assess the increase in discrimination of the augmented models.¹⁹ All statistical analyses were performed in STATA version 15.1 (Stata Corporation, College Station, TX, USA). Statistical significance was defined as a p-value of less than 0.05.

Results

Overall Results

A total of 18,234 patients from all of 81 provinces of Turkey were included in the final analyses. The geographic distribution of the patients according to provinces’ population was shown in **Supplemental Figure**. The mean (SD) age of the study population was 74.1 (7.4) and 53.4 % were women ($n = 9,736$). Hypertension (78.8%, $n = 14,376$), coronary artery disease (39.3%, $n = 7,175$), chronic obstructive pulmonary disease (35.9%, $n = 6,543$) and diabetes mellitus (36.2%, $n = 6,604$) were the most frequent comorbidities seen in the study population. Baseline demographics and clinical comorbidities were represented in **Table 1**.

Table 1
Baseline characteristics of patients according to mortality.

	Overall (n=18,234)	Survivors (n=14,919)	Non-survivors (n=3,315)	p value
Age, mean (SD)	74.1 (7.4)	73.4 (7.1)	77.4 (7.9)	<0.001
Sex, n(%)				
Female	9,736 (53.4%)	8,350 (56.0%)	1,386 (41.8%)	<0.001
Male	8,498 (46.6%)	6,569 (44.0%)	1,929 (58.2%)	
Comorbidities, n(%)				
Coronary Artery Disease	7,175 (39.3%)	5,582 (37.4%)	1,593 (48.1%)	<0.001
Coronary Artery Bypass Graft	295 (1.6%)	213 (1.4%)	82 (2.5%)	<0.001
Congestive Heart Failure	2,720 (14.9%)	1,851 (12.4%)	869 (26.2%)	<0.001
Valvular Heart Disease	408 (2.2%)	306 (2.1%)	102 (3.1%)	<0.001
Hypertension	14,376 (78.8%)	11,626 (77.9%)	2,750 (83.0%)	<0.001
Peripheral Vascular Disease	1,450 (8.0%)	1091 (7.3%)	359 (10.8%)	<0.001
Cerebrovascular Disease	3,446 (18.9%)	2,540 (17.0%)	906 (27.3%)	<0.001
Chronic Obstructive Pulmonary Disease	6,543 (35.9%)	5,209 (34.9%)	1,334 (40.2%)	<0.001
Diabetes Mellitus	6,604 (36.2%)	5,274 (35.4%)	1,330 (40.1%)	<0.001
Liver Disease	503 (2.8%)	388 (2.6%)	115 (3.5%)	0.006
Renal Failure	1,598 (8.8%)	1033 (6.9%)	565 (17.0%)	<0.001
Iron Deficiency Anemia	4,957 (27.2%)	4,026 (27.0%)	931 (28.1%)	0.20
Rheumatoid Disease	810 (4.4%)	668 (4.5%)	142 (4.3%)	0.62
Peptic Ulcer Disease	1381 (7.6%)	1126 (7.5%)	255 (7.7%)	0.78
Depression	3,971 (21.8%)	3,121 (20.9%)	850 (25.6%)	<0.001
Cancer	1,421 (7.8%)	1,037 (7.0%)	384 (11.6%)	<0.001
Substance Abuse	12 (0.1%)	7 (<1%)	5 (0.2%)	0.035
Alcohol Abuse	14 (0.1%)	10 (0.1%)	4 (0.1%)	0.31
Acquired Immunodeficiency Syndrome	2 (<1%)	2 (<1%)	0 (0.0%)	0.50
Hospital Frailty Risk Score, mean (SD)	8.9 (7.0)	8.4 (6.5)	11.6 (8.2)	<0.001
Frail (Hospital Frailty Risk Score >5), n(%)	12,295 (67.4%)	9,697 (65.0%)	2,598 (78.4%)	<0.001

Table 2
List of ICD-10-CM codes, number of points to create the Hospital Frailty Risk Score and prevalence according to mortality.

Codes	Definition	Point	Survivors n=14,919	Non-survivors n=3,315	p value
F00	Dementia in Alzheimer	7•1	657 (4.4%)	333 (10.0%)	<0.001
G81	Hemiplegia	4•4	209 (1.4%)	95 (2.9%)	<0.001
G30	Alzheimer's disease	4•0	976 (6.5%)	472 (14.2%)	<0.001
I69	Sequelae of cerebrovascular disease (secondary codes)	3•7	295 (2.0%)	146 (4.4%)	<0.001
R29	Other symptoms and signs involving the nervous and musculoskeletal systems (R29•6 Tendency to fall)	3•6	78 (0.5%)	20 (0.6%)	0.57
N39	Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	3•2	5,096 (34.2%)	1,244 (37.5%)	<0.001
F05	Delirium, not induced by alcohol and other psychoactive substances	3•2	194 (1.3%)	72 (2.2%)	<0.001
W19	Unspecified fall	3•2	1,077 (7.2%)	301 (9.1%)	<0.001
S00	Superficial injury of head	3•2	105 (0.7%)	28 (0.8%)	0.39
R31	Unspecified hematuria	3•0	345 (2.3%)	111 (3.3%)	<0.001
B96	Other bacterial agents as the cause of diseases classified to other chapters (secondary code)	2•9	37 (0.2%)	18 (0.5%)	0.005
R41	Other symptoms and signs involving cognitive functions and awareness	2•7	59 (0.4%)	20 (0.6%)	0.099
R26	Abnormalities of gait and mobility	2•6	175 (1.2%)	72 (2.2%)	<0.001
I67	Other cerebrovascular diseases	2•6	2,046 (13.7%)	734 (22.1%)	<0.001
R56	Convulsions, not elsewhere classified	2•6	9 (0.1%)	4 (0.1%)	0.24
R40	Somnolence, stupor and coma	2•5	16 (0.1%)	19 (0.6%)	<0.001
T83	Complications of genitourinary prosthetic devices, implants and grafts	2•4	1 (<1%)	0 (0.0%)	0.64
S06	Intracranial injury	2•4	31 (0.2%)	18 (0.5%)	<0.001
S42	Fracture of shoulder and upper arm	2•3	107 (0.7%)	28 (0.8%)	0.44
E87	Other disorders of fluid, electrolyte and acid-base balance	2•3	418 (2.8%)	244 (7.4%)	<0.001
M25	Other joint disorders, not elsewhere classified	2•3	5,465 (36.6%)	1,090 (32.9%)	<0.001
E86	Volume depletion	2•3	9 (0.1%)	4 (0.1%)	0.24
R54	Senility	2•2	644 (4.3%)	289 (8.7%)	<0.001
F03	Unspecified dementia	2•1	487 (3.3%)	249 (7.5%)	<0.001
W18	Other fall on same level	2•1	231 (1.5%)	56 (1.7%)	0.56
Z75	Problems related to medical facilities and other health care	2•0	124 (0.8%)	20 (0.6%)	0.18
F01	Vascular dementia	2•0	205 (1.4%)	89 (2.7%)	<0.001
S80	Superficial injury of lower leg	2•0	89 (0.6%)	20 (0.6%)	0.96
L03	Cellulitis	2•0	530 (3.6%)	168 (5.1%)	<0.001

The score presents the top 29 codes, each of which contributes ≥ 2 points. (All covariates are presented in Supplemental Table 2)

Hospital Frailty Risk Score

The top 29 ICD-10 codes of which contributes ≥2 points to HFRS are shown in **Table 2** (all covariates are presented in **Supplemental Table 2**).

The HFRS ranged from 0 to 53, with a mean (SD) HFRS of 8.9 (7.0). The distribution of the HFRS was presented in **Figure A**. A total of 2,801 (15.4%) patients were categorized in the highest level of frailty (HFRS of >15). Furthermore, 12,295 (67.4%) patients were defined as frail (HFRS of >5) (**Fig. 1**).

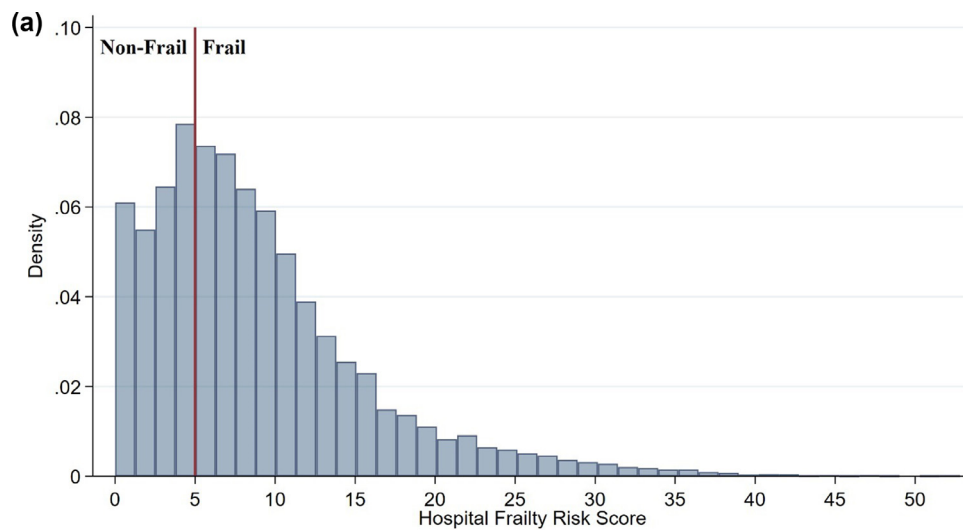
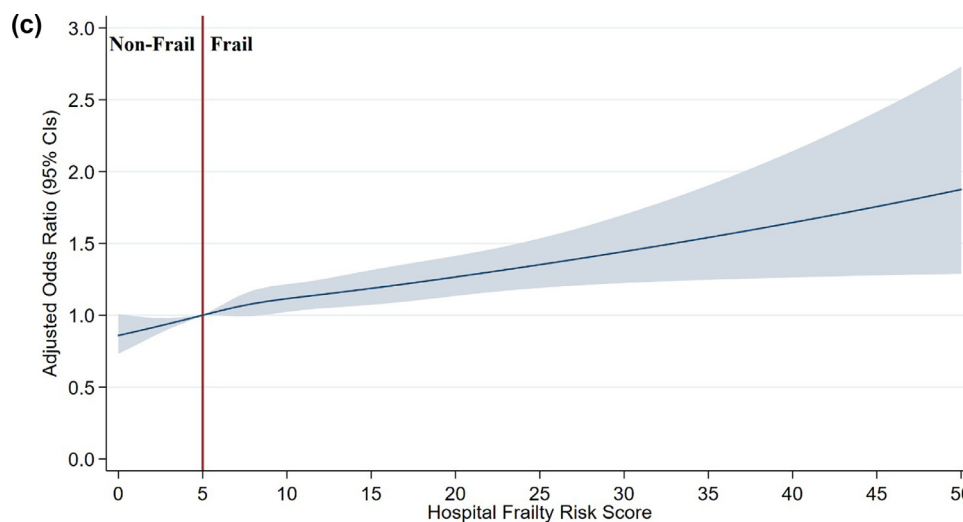
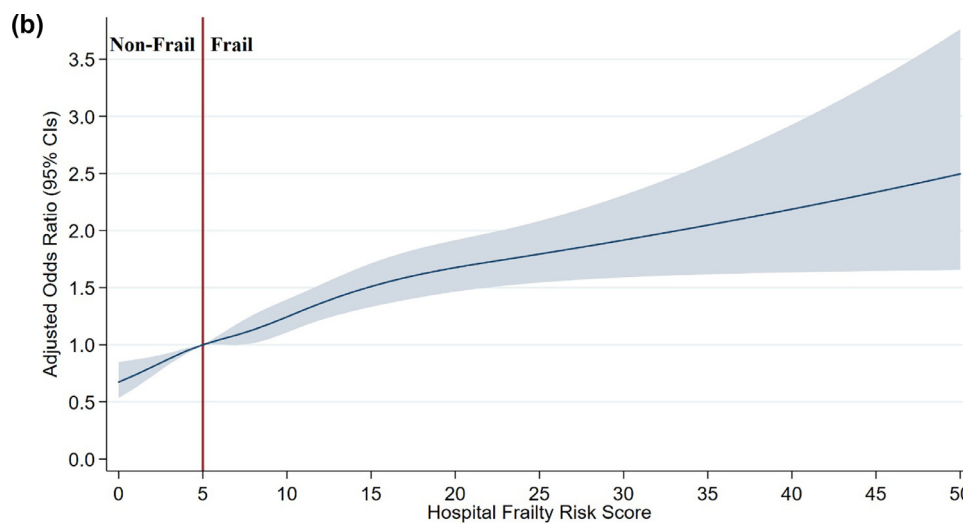


Fig. 1. Distribution of the HFERS among the study population and the association of the HFERS with outcomes (Red line indicates the cutoff score “5” for frailty).
 A. Distribution of the Hospital Frailty Risk Score among patients
 B. Mortality
 C. Long-length stay
 D. Intensive care unit
 E. Invasive mechanical ventilation



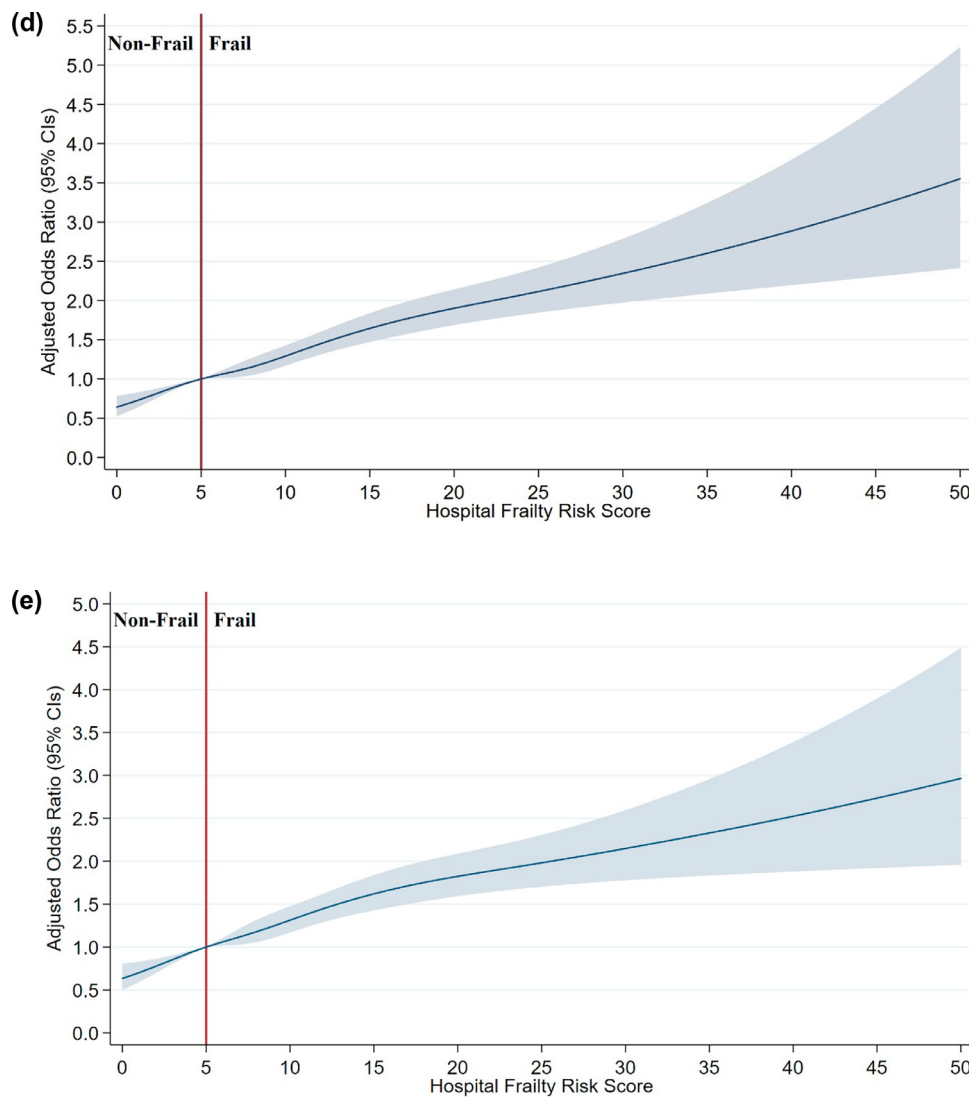


Fig. 1. Continued

Table 3
Outcomes of the Study Population According to Hospital Frailty Risk Score Categories.

	Overall n=18,234	Low Risk (<5) n=5,814 (31.9%)	Hospital Frailty Risk		p value
			Intermediate Risk (5-15) n=9,619 (52.8%)	High Risk (>15) n=2,801 (15.4%)	
Primary Outcome, n(%)					
All-cause Mortality	3,315 (18.2%)	697 (12.0%)	1,751 (18.2%)	867 (31.0%)	<0.001
Secondary Outcomes, n(%)					
Long-length stay, (> 10 days)	5,841 (32.0%)	1,695 (29.2%)	3,119 (32.4%)	1,027 (36.7%)	<0.001
Intensive care unit	4,510 (24.7%)	975 (16.8%)	2,397 (24.9%)	1,138 (40.6%)	<0.001
Invasive mechanical ventilation	3,080 (16.9%)	650 (11.2%)	1,653 (17.2%)	777 (27.7%)	<0.001

Study Outcomes

The primary outcome was observed in 3,315 (18.2%) patients. The in-hospital mortality rates were 12.0%, 18.2%, and 31.0% in low, intermediate, and high HFRS categories, respectively (p<0.001). Similarly, the secondary outcomes were also significantly higher in the high HFRS category as compared to moderate and low HFRS categories (p<0.001) (Table 3).

After adjustment for age, sex and comorbidities, the HFRS of >15 (compared with an HFRS of <5), was associated with a higher risk of in-hospital mortality (aOR, 2.084; 95% CI, 1.799-2.413, p<0.001), long-LOS (aOR, 1.317; 95% CI, 1.169-1.483, p<0.001), ICU (aOR, 2.221; 95% CI, 1.951-2.527, p<0.001), and invasive MV requirement rates (aOR, 1.769; 95% CI, 1.531-2.046, p<0.001). In sensitivity analyses, similar findings were observed when frailty assessed as a continuous scale (Table 4).

Table 4
Multivariable logistic regression analyses results.

	Adjusted Odds Ratio (95% CIs)	p value
All-cause Mortality		
Hospital Frailty Risk Score	1.036 (1.029-1.043)	<0.001
Hospital Frailty Risk Categories		<0.001
- Low risk (<5), reference	1.00	
- Intermediate-Risk (5-15)	1.482 (1.334-1.646)	
- High-Risk (>15)	2.084 (1.799-2.413)	
Long-length stay, (>10 days)		
Hospital Frailty Risk Score	1.016 (1.010-1.022)	<0.001
Hospital Frailty Risk Categories		<0.001
- Low risk (<5), reference	1.00	
- Intermediate-Risk (5-15)	1.152 (1.067-1.243)	
- High-Risk (>15)	1.317 (1.169-1.483)	
Intensive care unit		
Hospital Frailty Risk Score	1.041 (1.034-1.047)	<0.001
Hospital Frailty Risk Categories		<0.001
- Low Risk (<5), reference	1.00	
- Intermediate-Risk (5-15)	1.460 (1.334-1.598)	
- High-Risk (>15)	2.221 (1.951-2.527)	
Invasive mechanical ventilation		
Hospital Frailty Risk Score	1.031 (1.024-1.039)	<0.001
Hospital Frailty Risk Categories		<0.001
- Low Risk (<5), reference	1.00	
- Intermediate-Risk (5-15)	1.376 (1.240-1.527)	
- High-Risk (>15)	1.769 (1.531-2.046)	
<i>Models adjusted for age, sex, and comorbidities</i>		

Improvement in Risk Adjustment

After adding HFRS, discrimination, and performance of the models were significantly improved when assessed by DeLong and IDI tests for each outcome (Table 5). Besides, after adjustment for age, sex and comorbidities, primary and secondary outcomes rates [in-hospital mortality (Figure B); long-LOS (Figure C); ICU (Figure D); invasive MV requirement (Figure E)] monotonically increased with an increasing HFRS.

Discussion

To the best of our knowledge, this is the first research to demonstrate the usefulness of the HFRS for risk stratification at hospital admission in elderly patients with COVID-19. In our study, frailty, as determined by the HFRS, was associated with a higher risk of adverse outcomes including in-hospital mortality, long-LOS, the requirement of ICU, and invasive MV in elderly COVID-19 patients. Nearly 15% of COVID-19 patients were at the highest category of frailty. The addition of this ICD-10 claims-based frailty score significantly improved the prediction of both primary and secondary adverse outcomes when added to traditional comorbidities. Identifying older people with frailty and improving their care and support can be addressed by anticipatory guidance and early intervention to reduce high-risk clinical outcomes.

The COVID-19 pandemic has led to an unexpected and alarming load to the global healthcare systems worldwide. There was a debate in many countries about the prioritization of critical care for patients who will get the most benefit to save the highest number of lives.²⁰ Thus, it is crucial to determine who would benefit most from intensive care and ventilator support and allocation of scarce resources.²¹ However, this concept is both practically and ethically challenging.²² The different strategies have been adopted in different countries with selective admission of younger patients, and do-not-resuscitate labeling has highlighted the problem of “ageism”.¹²

Data from the United States and China showed that people aged older than 65 years represent half of the hospital admissions, more than half of the admissions to the ICU, and account for 80% of deaths related to COVID-19.^{23,24} Thus, it is clear that older people are at an increased risk for adverse outcomes due to COVID-19.^{1,2} However, contradictory study findings for elderly patients have also been reported in which older patients were discharged uneventfully.²⁵ Therefore, chronological age-based criteria alone for risk stratification and in the decision-making process of COVID-19 patients seem to be inadequate at best, misleading at worst, and a more comprehensive approach is necessary.^{2,4,26} The clinicians should consider baseline rather than the current status of patients with a critical illness.²⁷ Guidelines strongly suggest assessing the frailty for all elderly hospitalized patients.^{3,12,28} Thus, implementation of the frailty as an indicator of vulnerability has come back to our mind, especially for its ability to predict adverse outcomes in older patients with COVID-19.

In our study, we used the HFRS to assess the frailty in older COVID-19 patients which is a rapid, standardized, automated, and cost-efficient scale of frailty in hospitalized patients. This frailty scale brings more statistical power due to encompassing all patients rather than a selection of specific groups, the use of big data, and a large number of variables. It was internally and externally validated in several cohorts.^{16,29} However, its accuracy depends on the correct coding in the electronic recordings. There was no data about the role of HFRS in COVID-19 patients. Availability of a mandatory nationwide GHI and centralized national database all over Turkey was an advantage of our study to analyze big data in COVID-19 patients.

More than two-thirds of the included patients (67.2%) were frail in our study using HFRS which was higher than the recent multi-center study using the Clinical Frailty Scale (CFS) (49.2%) among the COVID-19 patients (COPE study).¹⁰ The difference primarily thought to be due to differences in study populations and methodology. In the COPE study, all-comers with COVID-19 aged ≥18 years have been included compared to enrolling aged ≥65 years in our study. Additionally, the CFS is based on the evaluation of patient abilities before two weeks from hospital admission.²⁹ Even if the CFS integrates items such as comorbidity, cognitive impairment, and disability³⁰ the HFRS could be a more useful screening tool since it is based on the longitudinal data derived from ICD-10 codes in patient’s 2-years prior medical history.¹⁶

Table 5
Discrimination of the models and the performance of improvement after adding frailty on outcomes.

	C-statistics without Hospital Frailty Risk Score	C-statistics with Hospital Frailty Risk Score	DeLong p-value	IDI (SE)	IDI p-value
Primary Outcome					
All-cause Mortality	0.70 (0.69-0.72)	0.73 (0.72-0.74)	<0.001	0.081 (0.006)	<0.001
Secondary Outcomes					
Long-length stay (>10 days)	0.59 (0.58-0.60)	0.61 (0.60-0.61)	0.045	0.012 (0.003)	<0.001
Intensive care unit	0.67 (0.66-0.68)	0.70 (0.69-0.70)	<0.001	0.080 (0.008)	<0.001
Invasive mechanical ventilation	0.66 (0.65-0.68)	0.68 (0.67-0.69)	<0.001	0.052 (0.007)	<0.001

IDI: Integrated Discrimination Improvement, SE: Standard Error

Mortality in our study was 18.2%, which was lower than the current mortality estimates ranged between 21 to 28.3% for COVID-19 globally.^{23,31} In a study from China including 1,099 patients with COVID-19 (15.1% aged of ≥ 65 years), the composite outcomes of ICU admission, invasive MV, and death were reported around 49.2%, but frailty has not been assessed.³² Despite a significant amount of requirement for ICU admission and invasive MV, the reasons for the relatively lower rate of mortality in our study might be explained by early capturing of patients at high risk living in care homes and living homes.³³ It also highlights the importance of more intense testing of caregivers to break transmission to the elderly and frail.³⁴

In the management of COVID 19, the detection of high-risk patients facilitates to plan an individualized therapy considering an early admission to ICU and also determines the comorbidities that may worsen the course of the disease and should be intervened if there is any reversible or correctable factor. In case of frailty caused by a reversible situation, the identification of these patients and further treatments with several targeted interventions can prevent the transition from the pre-frail condition to an entirely symptomatic, more vulnerable phase of frailty.³⁵ Based on the modified or reversed frailty parameters may directly translate into better treatment outcomes.^{35,36}

Limitations

Our study should be interpreted with some limitations. First, physiological measures of frailty, dynamic functional states, caregiver features, and temporal changes due to acute illness were not able to be captured in claims data. Therefore, the HFRS may not comprehensively measure frailty for all patients. Second, the HFRS can only be calculated after the first admission to the hospital. Third, it is also unclear whether the HFRS is a truly a measurement of frailty or complex comorbidity index. Fourth, the heterogeneity of the study population is another limitation of the study. Last, the administrative coding may misclassify some comorbidities and complications compared with prospective collection using standard clinical trial definitions.

Conclusion

The HFRS enables a standardized tool for clinicians and health care systems to detect and effectively stratify the frailty in elderly patients with COVID-19. Frailty-based tailored management of the older population may provide a more accurate risk categorization for both therapeutic and preventive strategies. Aware of the possibility of a second wave of COVID-19, immediate preparation is essential to overcome frailty since it is shown that adding frailty to age, sex, and baseline comorbidities significantly improved prognostic assessment.

Funding/Support

This study supported by Republic of Turkey Ministry of Health. The supporter had no role on design, analysis and interpretation.

Declaration of Competing Interest

Authors have no conflicts of interest to declare.

Acknowledgements

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.09.029.

References

- Moccia F, Gerbino A, Lionetti V, et al. COVID-19-associated cardiovascular morbidity in older adults: a position paper from the Italian Society of Cardiovascular Researches. *Geroscience* 2020.
- Bonnad C, Garcia-Blas S, Tarazona-Santabalbina FJ, et al. Coronavirus: the geriatric emergency of 2020. Joint document of the Section of Geriatric Cardiology of the Spanish Society of Cardiology and the Spanish Society of Geriatrics and Gerontology. *Rev Esp Cardiol (Engl Ed)* 2020.
- Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;**381**(9868):752–62.
- Boreskie KF, Boreskie PE, Melady D. Age is just a number - and so is frailty: Strategies to inform resource allocation during the COVID-19 pandemic. *CJEM* 2020:1–3.
- Moug S, Carter B, Myint PK, Hewitt J, McCarthy K, Pearce L. Decision-Making in COVID-19 and Frailty. *Geriatrics (Basel)* 2020;**5**(2).
- Kundi H, Wadhwa RK, Strom JB, et al. Association of Frailty With 30-Day Outcomes for Acute Myocardial Infarction, Heart Failure, and Pneumonia Among Elderly Adults. *JAMA Cardiol* 2019;**4**(11):1084–91.
- Kundi H, Popma JJ, Reynolds MR, et al. Frailty and related outcomes in patients undergoing transcatheter valve therapies in a nationwide cohort. *Eur Heart J* 2019;**40**(27):2231–9.
- Bellelli G, Rebora P, Valsecchi MG, Bonfanti P, Citerio G members C-MT Frailty index predicts poor outcome in COVID-19 patients. *Intensive Care Med* 2020.
- Chong E, Chan M, Tan HN, Lim WS. COVID-19: Use of the Clinical Frailty Scale for Critical Care Decisions. *J Am Geriatr Soc* 2020.
- Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. *Lancet Public Health* 2020.
- Aprahamian I, Cesari M. Geriatric Syndromes and SARS-Cov-2: More than Just Being Old. *J Frailty Aging* 2020;**9**(3):127–9.
- Maltese G, Corsonello A, Di Rosa M, et al. Frailty and COVID-19: A Systematic Scoping Review. *Journal of Clinical Medicine* 2020;**9**(7).
- De Smet R, Mellaerts B, Vandewinckele H, et al. Frailty and mortality in hospitalized older adults with COVID-19: retrospective observational study. *Journal of the American Medical Directors Association* 2020.
- Demirel D. E-HEALTH APPLICATIONS in TURKEY. *Pressacademia* 2017;**4**(1):422–32.
- Demirbilek Y, Pehlivanurk G, Ozguler ZO, Alp Mese E. COVID-19 outbreak control, example of ministry of health of Turkey. *Turk J Med Sci* 2020;**50**(SI-1):489–94.
- Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *The Lancet* 2018;**391**(10132):1775–82.
- Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA* 1982;**247**(18):2543–6.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**(3):837–45.
- Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;**27**(2):157–72 discussion 207–12.
- Leclerc T, Donat N, Donat A, et al. Prioritisation of ICU treatments for critically ill patients in a COVID-19 pandemic with scarce resources. *Anaesth Crit Care Pain Med* 2020.
- Mannelli C. Whose life to save? Scarce resources allocation in the COVID-19 outbreak. *J Med Ethics* 2020;**46**(6):364–6.
- Chase J. Caring for Frail Older Adults During COVID-19: integrating public health ethics into clinical practice. *J Am Geriatr Soc* 2020.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**(10229):1054–62.
- Team CC-R. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**(12):343–6.
- Dowd JB, Andriano L, Brazel DM, et al. Demographic science aids in understanding the spread and fatality rates of COVID-19. *Proc Natl Acad Sci U S A* 2020;**117**(18):9696–8.
- Cesari M, Montero-Odasso M. COVID-19 and Older Adults. Lessons Learned from the Italian Epicenter. *Can Geriatr J* 2020;**23**(1):155–9.
- Flaatten H, Clegg A. Frailty: we need valid and reliable tools in critical care. *Intensive Care Med* 2018;**44**(11):1973–5.
- NICE. COVID-19 rapid guideline: critical care in adults. <https://www.nice.org.uk/guidance/ng159/chapter/2-Admission-to-critical-care> 2020.
- McAlister F, van Walraven C. External validation of the Hospital Frailty Risk Score and comparison with the Hospital-patient One-year Mortality Risk Score to predict outcomes in elderly hospitalised patients: a retrospective cohort study. *BMJ Qual Saf* 2019;**28**(4):284–8.

30. O’Caoimh R, Kennelly S, Ahern E, O’Keeffe S, Ortuno RR. Letter to the Editor: Covid-19 and the Challenges of Frailty Screening in Older Adults. *J Frailty Aging* 2020;**9**(3):185–6.
31. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020.
32. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020;**382**(18):1708–20.
33. Bigelow BF, Tang O, Barshick B, et al. Outcomes of Universal COVID-19 Testing Following Detection of Incident Cases in 11 Long-term Care Facilities. *JAMA Internal Medicine* 2020.
34. Altringer L, Zahran S, Prasad A. The Longevity-Frailty Hypothesis: Evidence from COVID-19 Death Rates in Europe. *medRxiv* 2020 2020.04.14.20065540.
35. Wleklík M, Uchmanowicz I, Jankowska EA, et al. Multidimensional Approach to Frailty. *Front Psychol* 2020;**11**:564.
36. Ceravolo MG, De Sire A, Andrenelli E, Negrini F, Negrini S. Systematic rapid "living" review on rehabilitation needs due to covid-19: update to march 31st 2020. *Eur J Phys Rehabil Med* 2020.