Association between Clinical Frailty Scale score and hospital mortality in adult patients with COVID-19 (COMET) an international, multicentre, retrospective, observational cohort study

Sablerolles, R.S.G.; Lafeber, M.; Kempen, J.A.L. van; Loo, B.P.A. van de; Boersma, E.; Rietdijk, W.J.R.; ... ; COMET Res Team

Association between Clinical Frailty Scale score and hospital mortality in adult patients with COVID-19 (COMET): an international, multicentre, retrospective, observational cohort study

*Roos S G Sablerolles, Melvin Lafeber, Janneke A L van Kempen, Bob P A van de Loo, Eric Boersma, Wim J R Rietdijk, Harmke A Polinder-Bos, Simon P Mooijaart, Hugo van der Kuy, Jorie Versmissen, Miriam C Faes, on behalf of the COMET research team**

Summary

Background During the COVID-19 pandemic, the scarcity of resources has necessitated triage of critical care for patients with the disease. In patients aged 65 years and older, triage decisions are regularly based on degree of frailty measured by the Clinical Frailty Scale (CFS). However, the CFS could also be useful in patients younger than 65 years. We aimed to examine the association between CFS score and hospital mortality and between CFS score and admission to intensive care in adult patients of all ages with COVID-19 across Europe.

Methods This analysis was part of the COVID Medication (COMET) study, an international, multicentre, retrospective observational cohort study in 63 hospitals in 11 countries in Europe. Eligible patients were aged 18 years and older, had been admitted to hospital, and either tested positive by PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or were judged to have a high clinical likelihood of having SARS-CoV-2 infection by the local COVID-19 expert team. CFS was used to assess level of frailty: fit ($CFS_{1–3}$), mildly frail ($CFS_{4–5}$), or frail ($CFS_{6–9}$). The primary outcome was hospital mortality. The secondary outcome was admission to intensive care. Data were analysed using a multivariable binary logistic regression model adjusted for covariates (age, sex, number of drugs prescribed, and type of drug class as a proxy for comorbidities).

Findings Between March 30 and July 15, 2020, 2434 patients (median age 68 years [IQR 55–77]; 1480 [61%] men, 954 [30%] women) had CFS scores available and were included in the analyses. In the total sample and in patients aged 65 years and older, frail patients and mildly frail patients had a significantly higher risk of hospital mortality than fit patients (total sample: $CFS_{6–9}$ *vs* $CFS_{1–3}$ odds ratio [OR] 2·71 [95% CI 2·04–3·60], p<0·0001 and $CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 1·54 [1·16–2·06], p=0·0030; age ≥65 years: $CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 2·90 [2·12–3·97], p<0·0001 and $CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 1·64 [1·20–2·25], p=0·0020). In patients younger than 65 years, an increased hospital mortality risk was only observed in frail patients ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 2·22 [1·08–4·57], p=0·030; $CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 1·08 [0·48–2·39], p=0·86). Frail patients had a higher incidence of admission to intensive care than fit patients ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 1·54 [1·21–1·97], p=0·0010), whereas mildly frail patients had a lower incidence than fit patients ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 0·71 [0·55–0·92], p=0·0090). Among patients younger than 65 years, frail patients had an increased incidence of admission to intensive care ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 2·96 [1·98–4·43], p<0·0001), whereas mildly frail patients had no significant difference in incidence compared with fit patients ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 0·93 [0·63–1·38], p=0·72). Among patients aged 65 years and older, frail patients had no significant difference in the incidence of admission to intensive care compared with fit patients ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 1·27 [0·92–1·75], p=0·14), whereas mildly frail patients had a lower incidence than fit patients ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 0·66 [0·47–0·93], p=0·018).

Interpretation The results of this study suggest that CFS score is a suitable risk marker for hospital mortality in adult patients with COVID-19. However, treatment decisions based on the CFS in patients younger than 65 years should be made with caution.

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*Members are listed in the appendix (pp 9–10)

Department of Internal Medicine (R S G Sablerolles MD, M Lafeber MD, J Versmissen MD), **Department of Cardiology** (Prof E Boersma PhD), **Department of Hospital Pharmacy** (W J R Rietdijk PhD, Prof H van der Kuy PharmD, J Versmissen), **and Department of Geriatrics** (H A Polinder-Bos MD) **Erasmus MC, University Medical Centre Rotterdam, Rotterdam, Netherlands; Department of Geriatrics, Amphia Hospital, Breda, Netherlands** (J A L van Kempen MD, M C Faes MD); **Digitalis Rx BV, Amsterdam, Netherlands** (B P A van de Loo Msc); **Department of Gerontology and Geriatrics, Leiden University Medical Centre, Leiden, Netherlands** (S P Mooijaart MD)

Correspondence to: Prof Hugo van der Kuy, Department of Hospital Pharmacy, Erasmus MC, University Medical Centre Rotterdam, 3015 GD Rotterdam, Netherlands **h.vanderkuy@erasmusmc.nl**

See Online for appendix

Introduction

During the COVID-19 pandemic, the scarcity of resources necessitated triage of critical care for patients with COVID-19.[1] Triage decisions for critical care in older patients outside of the COVID-19 pandemic are regularly made on the basis of the degree of frailty.[2–5] Frailty is a condition with a high prevalence in older people and is characterised by a decline in multiple physiological systems and increased vulnerability to stressors.[6] Frailty is related to adverse health outcomes, such as falls,

Research in context

Evidence before this study

We searched PubMed for clinical studies published in English between Jan 1, 2005, and Jan 10, 2021. The following search terms were used: ("COVID-19" OR "SARS-CoV-2" OR "corona virus") AND "CFS" OR "Clinical Frailty Scale" OR "Clinical Frailty Score" OR "frailty") AND ("intensive care" OR "mortality" OR "survival") to find studies evaluating frailty and the Clinical Frailty Scale (CFS) in acutely ill patients. To examine the association between the score on the CFS and hospital mortality in patients with COVID-19 across Europe, we searched for studies that compared associations between frailty and hospital mortality in older patients with COVID-19. Finally, we also used (European) guidelines that provide advice on how to deal with intensive care policy in the COVID-19 pandemic. Based on this search, we found that older people with frailty have an increased risk of dying from COVID-19. However, there is a gap in the literature regarding whether these results also apply to frail patients younger than 65 years.

Added value of this study

The conclusions of this study are based on data from 63 hospitals in 11 European countries. Frail (CFS score 6–9) adult patients of all ages with COVID-19 have an increased risk of hospital mortality compared with patients who are not frail. These results indicate that CFS score is a suitable risk marker for hospital mortality in patients with COVID-19.

Implications of all the available evidence

This study shows that CFS score is a suitable risk marker for hospital mortality in adult patients of all ages with COVID-19. However, treatment decisions based on CFS scores in patients younger than 65 years should be made with caution.

functional decline, hospital admissions, and mortality.[7] For the purpose of triage, frailty is often measured by the Clinical Frailty Scale (CFS), which could improve the prediction of adverse outcomes of frailty.[2–5]

The association of frailty and mortality in patients aged 65 years or older with COVID-19 is described in several previous studies.[8–13] For example, Hewitt and colleagues[8] and Aw and colleagues[11] showed in their prospective studies that frailty was associated with mortality in patients with COVID-19, although, in a much smaller prospective study by Miles and colleagues,[13] no evidence was found for this association. Furthermore, in the retrospective study by Owen and colleagues,[12] no association was observed between frailty and mortality in patients with COVID-19, although the data were from a small sample of patients. In a retrospective study with 18 000 patients among all hospitals in Turkey, Kundi and colleagues[14] showed that frailty was associated with a higher risk of hospital mortality in patients with COVID-19. However, frailty was measured by the Hospital Frailty Risk Score (HFRS), which is based on International Classification of Diseases 10 codes. The authors questioned whether the HFRS is truly an indicator of frailty or a complex comorbidity index. In short, except for Hewitt and colleagues,[8] most of the studies using the CFS to measure frailty are limited to single-centre data and have a small sample of patients. This signifies that more data are required to robustly assess the association between frailty and mortality in patients with COVID-19. Furthermore, the CFS has only been validated in samples of older (≥65 years) patients.[1,6] However, the widely used CFS might also be relevant in younger patients with COVID-19. Several studies have applied the CFS in younger populations with COVID-19; for example, Aw and colleagues[11] used the CFS in a population of patients aged 18 years and older with COVID-19, but only analysed the data in patients aged 65 years and older. Hewitt and colleagues[8] showed in a subanalysis in patients younger than 65 years with COVID-19 that frailty (CFS score of 5–7 [$CFS_{5–7}$]) was associated with a higher mortality by day 7 than non-frailty (CFS score of 1–4 [$CFS_{1–4}$]; appendix p 11). In an earlier study from Hewitt and colleagues,[15] in which patients aged 18 years and older without COVID-19 were admitted to an acute surgical unit, it was shown that worsening frailty was associated with significantly poorer patient outcomes, including mortality. Finally, a study by Darvall and colleagues[16] found that only severe and very severe frailty scores (CFS score of 7–8 [$CFS_{7–8}$]) were associated with mortality in patients aged 16 years and older who were admitted to an intensive care unit with pneumonia (without COVID-19).

In the context of COVID-19, national guidelines use different thresholds for frailty and admissibility to an intensive care unit.[17–19] The National Institute for Health and Care Excellence (NICE) published COVID-19 rapid guidelines in March, 2020, and recommended the use of the CFS to determine whether or not patients aged 65 years and older were candidates for admission to an intensive care unit. For patients younger than 65 years, NICE suggested that an individualised assessment is done and that the CFS is not used.[17] However, due to the enormous pressure of COVID-19 on health-care systems, it is important to have access to instruments, such as the CFS, to support health-care professionals in identifying patient subgroups and to make critical care triage decisions.

For these reasons, the aim of this study was to assess the association between CFS score and hospital mortality in patients of any age with COVID-19, as well as in patients younger than 65 years and patients aged 65 years and older. As a secondary aim, we investigated the association between CFS score and incidence of admission to intensive care in these patients.

Methods

Study design and participants

The COVID Medication (COMET) study is an international, multicentre, retrospective, observational cohort study done in 63 hospitals in 11 countries in Europe (appendix pp 9–10). The rationale and design of the COMET study have previously been described in detail.[20] In summary, patients were enrolled by pharmacists, clinical pharmacologists, or treating physicians at each centre. All participating investigators consecutively included those patients aged 18 years and older who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and were admitted to the clinical wards during the first wave of the COVID-19 pandemic (March–July, 2020). The major criterion for a patient to be included in the study was SARS-CoV-2 positive status by PCR, or a high clinical likelihood of COVID-19 based on bilateral pulmonary infiltrates not explained otherwise, or after consensus by the local COVID-19 expert team, based on clinical, biochemical, and radiological criteria. Written, informed consent was not required. The institutional review committee of the main site, the Erasmus MC in the Netherlands, approved the study (MEC-2020-0277), and each institutional review board of the participating hospitals approved the use of data, as described in the protocol.[20] All data were treated according to the European privacy regulations and the study was done in accordance with the Declaration of Helsinki.[21]

Data collection

Because enrolment took place during the first wave of COVID-19 infections, we had limited time to choose a pragmatic design for this study. Therefore, data collection focused on prescribed medication, patient and admission characteristics, and clinical outcomes. The follow-up period is defined as the time between hospital admission and either discharge or death. The dataset for the present study was closed Oct 3, 2020.

The focus of the current analysis was the CFS (for details of the CFS categories see appendix p 11), as scored by the treating physician. The CFS bases the frailty assessment on how a patient functioned 2 weeks before hospital admission. The CFS is an ordinal hierarchical scale that numerically ranks frailty on a scale 1–9, with a score of 1 being very fit, 2 well, 3 managing well, 4 vulnerable, 5 mildly frail, 6 moderately frail, 7 severely frail, 8 very severely frail, and 9 terminally ill. The following additional variables were collected: year of birth, sex, prescribed medication by Anatomical Therapeutic Chemical code, admission to intensive care, and hospital mortality. Comorbidity was indicated to be an important covariate of the relation between frailty and mortality and was therefore used as a covariate in the analysis. Because the entry of details of comorbid disease from patient records is time consuming and often incomplete, data on type of drugs prescribed served as a proxy for comorbidities: atherosclerotic cardiovascular disease (ie, coronary artery disease, cerebrovascular disease, or peripheral artery occlusive disease) was considered present if antiplatelet drugs were prescribed; atrial fibrillation or venous thromboembolism was considered present if oral anticoagulant drugs were prescribed; hypertension was considered present if blood pressure-lowering drugs were prescribed; and diabetes was considered present if glucose-lowering drugs or insulin was prescribed. Although not all patients with dementia use cholinesterase inhibitors or antipsychotic drugs for the treatment of behavioural or psychological symptoms of dementia, we used these as the best available proxy, as we considered dementia to be an important covariate.[22]

Data were collected in an online database (Clinical Rules reporter, version 1.6.3; Digitalis Rx, Amsterdam, Netherlands). A study number was assigned to each participating patient. The coding file was only available to the local investigator.

Outcomes

The primary outcome was hospital mortality. The secondary outcome was admission to an intensive care unit at any time during the hospital stay.

Statistical analysis

Because the aim of the study was to include as many patients from as many centres in Europe as possible, we did not do a power calculation on the minimum sample size. Descriptive statistics (n [%] or median [IQR]) were used for the characteristics of patients in the total study sample, the characteristics of patients within each category of CFS score, and the characteristics of patients younger than 65 years and aged 65 years and older. The three categories of CFS score were defined as fit patients ($CFS_{1–3}$), mildly frail patients ($CFS_{4–5}$), and frail patients ($CFS_{6–9}$). Fit patients were used as the reference category.

Because CFS was not scored in all enrolled individuals, characteristics of the subgroup of patients with a CFS score in the COMET dataset was compared with the subgroup of patients with a missing CFS score. Statistically significant differences in the baseline characteristics were examined using the Mann-Whitney *U* test for continuous variables and χ^2 for categorical variables. Differences in these characteristics were also assessed between the two age groups (<65 and ≥65 years) and between the three CFS score categories ($CFS_{1–3}$, $CFS_{4–5}$, and $CFS_{6–9}$). When comparing the characteristics between the two age groups we used a Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. When comparing these characteristics between the three CFS score categories we used a one-way ANOVA for continuous variables and Fisher's exact test for categorical variables.

For the primary outcome (ie, hospital mortality), a multivariable binary logistic regression model was used to analyse the data. The regression models were built up as

follows: an initial model estimating a crude, unadjusted estimate (model I); then with adjustment for age and sex (model II); then with additional adjustment for the number of drugs used by the patient (model III); and further adjustment for concomitant drugs (antiplatelet drugs, oral anticoagulant drugs, blood pressure-lowering drugs, glucose-lowering drugs, insulin, and cholinesterase inhibitors or antipsychotic drugs; model IV). Estimates were presented as odds ratios (OR) with 95% CI and p values. A two-tailed probability value of less than 0·05 was used as the criterion for statistical significance. For the secondary outcome (ie, admission to intensive care), the data were analysed in the same way as the primary outcome. The primary and secondary outcomes were assessed in all patients for whom a CFS score was known.

Three sensitivity analyses were also done. The first sensitivity analysis examined the linear association between CFS score and hospital mortality, and between CFS score and admission to intensive care, using the same binary logistic regression models. Here, CFS score was used as a continuous variable rather than stratified into three categories. A second sensitivity analysis was the binary logistic regression model IV including body-mass index as an additional covariate. Body-mass index was put into three categories: normal (<25), pre-obese (25–29·9), and obese (≥30). A third sensitivity analysis examined the association between CFS score and hospital mortality, it was stratified for whether the patient required admission to intensive care or not during the COVID-19 hospitalisation. All analyses were done using SPSS, version 25.0.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 30 and July 15, 2020, 5536 patients with COVID-19 were added to the database; the CFS was completed for 2434 (Austria n=447, Belgium n=46, Denmark n=30, France n=71, Germany n=12, the UK n=53, Italy n=327, the Netherlands n=1030, Portugal n=148, Spain n=179, and Switzerland n=91; 44%) patients, all of whom were included in the analyses of the primary and secondary endpoints.

Baseline characteristics of the 2434 included patients are shown in table 1; baseline characteristics of the patients grouped by age (<65 and ≥65 years) and by CFS score category ($CFS_{1–3}$, $CFS_{4–5}$, $CFS_{6–9}$) are shown in table 2 and the appendix (pp 2–3; p values in the appendix shown for reference only). In general, frail patients ($CFS_{6–9}$) were older (median 75 years [IQR 65–84] *vs* 62 years [51–72]) and were prescribed more drugs (median 5 [2–9] *vs* 2 [1–6]) than fit patients ($CFS_{1–3}$; appendix p 3). Patients with a missing CFS score were significantly older (median age 69 years [IQR 58–78] *vs* 67 years [55–77], p<0·0001) and were prescribed significantly more drugs (median 5 [2–9] *vs* 3 [1–7], p<0·0001) than patients with a CFS score. Mortality was significantly higher in patients without CFS scores than in patients with CFS scores (653 [21%] of 3102 *vs* 456 [19%] of 2423, p=0·032); however, intensive care unit admissions did not differ between these two groups of patients (700 [23%] of 3102 without CFS scores *vs* 616 [25%] of 2434 with CFS scores, p=0·13). The results of this additional analysis are in the appendix (p 1).

The association between CFS score and hospital mortality is shown in table 3. After adjustment for available covariates (model IV), frail patients and mildly frail patients had an increased risk of hospital mortality, irrespective of age ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 2·71 [95% CI 2·04–3·60], p<0·0001; $CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 1·54 [1·16–2·06], p=0·0030) within the total sample. In patients aged 65 years and older, after adjustment for all covariates (model IV) frail patients and mildly frail patients had an increased risk of hospital mortality compared with patients who were fit ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 2·90 [95% CI 2·12–3·97], p<0·0001; $CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 1·64 [1·20–2·25], p=0·0020), whereas in patients

	All patients (n=2434)
Age, years	67 (55–77)
<65	1096 (45%)
65–75	589 (24%)
>75	749 (31%)
Sex	
Male	1480 (61%)
Female	954 (30%)
Concomitant drugs	
Blood pressure-lowering drugs	1136 (47%)
Antiplatelet drugs	405 (17%)
Oral anticoagulant drugs	272 (11%)
Glucose-lowering drugs	437 (18%)
Antipsychotic drugs and cholinesterase inhibitors	143 (6%)
Number of prescribed drugs	3 (1–7)
Clinical Frailty Score	
1 very fit	253 (10%)
2 well	677 (28%)
3 managing well	447 (18%)
4 vulnerable	366 (15%)
5 mildly frail	198 (8%)
6 moderately frail	182 (7%)
7 severely frail	194 (8%)
8 very severely frail	99 (4%)
9 terminally ill	18 (1%)
Clinical outcome	
Hospital mortality	456 (19%)
Intensive care unit admission	616 (25%)

Data are median (IQR) or n (%). Percentages have been rounded and might not total 100%.

Table 1: **Baseline characteristics of the total sample**

	CFS score 1–3 (fit)		CFS score 4–5 (mildly frail)		CFS score 6–9 (frail)	
	Age <65 years (n=792)	Age ≥65 years (n=585)	Age <65 years (n=179)	Age ≥65 years (n=385)	Age <65 years (n=125)	Age ≥65 years (n=368)
Age, years	53 (44–60)	74 (69–79)	54 (45–59)	78 (73–84)	56 (49–60)	79 (73–86)
Sex						
Male	491 (62%)	362 (62%)	121 (68%)	208 (54%)	88 (70%)	210 (57%)
Female	301 (38%)	223 (38%)	58 (32%)	177 (46%)	37 (30%)	158 (43%)
Concomitant drugs						
Blood pressure-lowering drugs	187 (24%)	350 (60%)	50 (28%)	254 (66%)	48 (38%)	247 (67%)
Antiplatelet drugs	50 (6%)	129 (22%)	17 (9%)	105 (27%)	14 (11%)	90 (24%)
Oral anticoagulant drugs	21 (3%)	95 (16%)	3 (2%)	69 (18%)	8 (6%)	76 (21%)
Glucose-lowering drugs	77 (10%)	121 (21%)	27 (15%)	104 (27%)	26 (21%)	82 (22%)
Antipsychotic drugs and cholinesterase inhibitors	13 (2%)	24 (4%)	7 (4%)	30 (8%)	5 (4%)	64 (17%)
Number of prescribed drugs	1 (1–4)	4 (2–7)	1 (1–5)	6 (3–9)	3 (1–6)	6 (3–9)
Outcome						
Hospital mortality	30 (4%)	112 (19%)	10 (6%)	122 (32%)	13 (10%)	169 (46%)
Intensive care unit admission	187 (24%)	166 (28%)	41 (23%)	63 (16%)	62 (50%)	97 (26%)

Data are median (IQR) or n (%). CFS=Clinical Frailty Scale.

Table 2: **Baseline characteristics for patients stratified by age and CFS score category**

younger than 65 years, there was only an increased risk of hospital mortality in frail patients ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 2·22 [1·08–4·57], p=0·030). For mildly frail patients younger than 65 years there was no significantly increased risk of hospital mortality ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 1·08 [0·48–2·39], p=0·86).

The association between CFS score and admission to an intensive care unit is shown in table 4. After adjusting for available covariates (model IV), irrespective of age, frail patients had a significantly increased incidence of admission to intensive care compared with fit patients ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 1·54 [95% CI 1·21–1·97], p=0·0010). Compared with fit patients, mildly frail patients had a decreased incidence of admission to intensive care ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 0·71 [0·55–0·92], p=0·0090). Among patients younger than 65 years, frail patients had an increased incidence of admission to intensive care ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 2·96 [1·98–4·43], p<0·0001), whereas mildly frail patients had no significant difference in the incidence of admission to intensive care compared with fit patients ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 0·93 [0·63–1·38], p=0·72). Among patients aged 65 years and older, frail patients had no significant difference in the incidence of admission to intensive care compared with fit patients ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 1·27 [0·92–1·75], p=0·14), whereas mildly frail patients had a decreased incidence of admission to intensive care ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 0·66 [0·47–0·93], p=0·018; table 4). The full regression estimates of the models are in the appendix (pp 4–5).

Three sensitivity analyses were done. First, the association between the continuous CFS and the clinical outcomes was analysed (appendix p 6). The results from model IV showed that there were positive and significant associations between continuous CFS scores and hospital mortality (OR 1·27 [95% CI 1·20–1·35]) and incidence of admission to intensive care (OR 1·12 [1·07–1·18]).

Second, the binary logistic regression models were repeated with body-mass index as an additional covariate in the model for hospital mortality and admission to intensive care (appendix p 7). Because not all patients were weighed at the emergency department, we did this analysis with a smaller sample of patients (all those with weight and height data available: hospital mortality

	CFS score 1–3 (fit)	CFS score 4–5 (mildly frail)	p value	CFS score 6–9 (frail)	p value
Total sample (number of events 456)					
Model I	1 (ref)	2·66 (2·05–3·46)	<0·0001	5·35 (4·15–6·90)	<0·0001
Model II	1 (ref)	1·64 (1·23–2·19)	0·0010	2·98 (2·25–3·94)	<0·0001
Model III	1 (ref)	1·55 (1·16–2·06)	0·0030	2·80 (2·11–3·71)	<0·0001
Model IV	1 (ref)	1·54 (1·16–2·06)	0·0030	2·71 (2·04–3·60)	<0·0001
Age <65 years (number of events 53)					
Model I	1 (ref)	1·49 (0·72–3·11)	0·29	3·17 (1·60–6·28)	0·0010
Model II	1 (ref)	1·46 (0·69–3·06)	0·32	2·69 (1·35–5·38)	0·0050
Model III	1 (ref)	1·14 (0·53–2·48)	0·74	2·15 (1·05–4·41)	0·036
Model IV	1 (ref)	1·08 (0·48–2·39)	0·86	2·22 (1·08–4·57)	0·030
Age ≥65 years (number of events 403)					
Model I	1 (ref)	1·96 (1·46–2·65)	<0·0001	3·70 (2·76–4·96)	<0·0001
Model II	1 (ref)	1·71 (1·25–2·34)	0·0010	3·11 (2·28–4·23)	<0·0001
Model III	1 (ref)	1·64 (1·20–2·24)	0·0020	2·97 (2·18–4·05)	<0·0001
Model IV	1 (ref)	1·64 (1·20–2·25)	0·0020	2·90 (2·12–3·97)	<0·0001

Estimates are odds ratio (95% CI). CFS=Clinical Frailty Scale. Model I=crude. Model II=adjusted for sex and age. Model III=model II plus additional adjustment for number of drugs used. Model IV=model III plus additional adjustment for blood pressure-lowering drugs, antiplatelet drugs, oral anticoagulant drugs, glucose-lowering drugs, antipsychotic drugs, and cholinesterase inhibitors.

Table 3: **Hospital mortality (primary outcome)**

	CFS score 1–3 (fit)	CFS score 4–5 (mildly frail)	p value	CFS score 6–9 (frail)	p value
Total sample (events n=616)					
Model I	1 (ref)	0·67 (0·52–0·85)	0·0010	1·38 (1·11–1·73)	0·0050
Model II	1 (ref)	0·69 (0·54–0·89)	0·0050	1·45 (1·14–1·84)	0·0020
Model III	1 (ref)	0·71 (0·55–0·92)	0·0090	1·50 (1·18–1·91)	0·0010
Model IV	1 (ref)	0·71 (0·55–0·92)	0·0090	1·54 (1·21–1·97)	0·0010
Age <65 years (events n=290)					
Model I	1 (ref)	0·97 (0·66–1·43)	0·89	3·23 (2·19–4·76)	<0·0001
Model II	1 (ref)	0·93 (0·63–1·38)	0·72	2·88 (1·94–4·29)	<0·0001
Model III	1 (ref)	0·94 (0·64–1·40)	0·77	2·94 (1·96–4·39)	<0·0001
Model IV	1 (ref)	0·93 (0·63–1·38)	0·72	2·96 (1·98–4·43)	<0·0001
Age ≥65 years (events n=326)					
Model I	1 (ref)	0·50 (0·36–0·69)	<0·0001	0·90 (0·67–1·21)	0·48
Model II	1 (ref)	0·63 (0·45–0·89)	0·0080	1·19 (0·87–1·63)	0·27
Model III	1 (ref)	0·66 (0·47–0·93)	0·016	1·25 (0·91–1·72)	0·16
Model IV	1 (ref)	0·66 (0·47–0·93)	0·018	1·27 (0·92–1·75)	0·14

Estimates are odds ratio (95% CI). CFS=Clinical Frailty Scale. Model I=crude. Model II=adjusted for sex and age. Model III=model II plus additional adjustment for number of drugs used. Model IV=model III plus additional adjustment for blood pressure-lowering drugs, antiplatelet drugs, oral anticoagulant drugs, glucose-lowering drugs, antipsychotic drugs, and cholinesterase inhibitors.

Table 4: **Admission to intensive care (secondary outcome)**

1882 [77·3%] of 2434 patients; admission to intensive care 1929 [79·3%] of 2434). Although the sample is smaller, the conclusions from this sensitivity analysis are similar to the results from our main analysis.

Third, the association between categories of CFS score and hospital mortality was analysed and stratified for whether the patient was admitted to an intensive care unit while hospitalised for COVID-19. Frail patients who were admitted to intensive care were significantly more likely to die in hospital than fit patients who were admitted to intensive care ($CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 1·81 [95% CI 1·14–2·87]; appendix p 8). There was no significant difference in hospital mortality between mildly frail patients and fit patients who were admitted to intensive care ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 1·33 [95% CI 0·78–2·27]). For patients who were not admitted to intensive care, both mildly frail patients and frail patients were significantly more likely to die in hospital than fit patients ($CFS_{4–5}$ *vs* $CFS_{1–3}$ OR 1·90 [95% CI 1·31–2·75]; $CFS_{6–9}$ *vs* $CFS_{1–3}$ OR 3·23 [2·22–4·72]; appendix p 8).

Discussion

This international, multicentre, retrospective, observational cohort study aimed to investigate the associations between CFS scores and hospital mortality and admission to intensive care in a large sample of patients with COVID-19. The results show that frail patients ($CFS_{6–9}$) of all ages admitted with COVID-19 had significantly higher hospital mortality than fit patients ($CFS_{1–3}$).

There are several prospective and retrospective studies investigating the association of frailty, measured by the CFS, with hospital mortality for patients aged 65 years and older with COVID-19.[8–13]

The prospective study by Miles and colleagues[13] showed no significant association between CFS score and hospital mortality, whereas the prospective studies by Hewitt and colleagues[8] and Aw and colleagues[11] showed that frailty was associated with mortality. The study by Hewitt and colleagues[8] was done in a large international cohort of around 1500 patients, whereas the study by Miles and colleagues[13] only included 212 patients from a single centre and might be underpowered to detect such an association.

A retrospective study by Owen and colleagues[12] was based on single-centre data. In this study, no significant association between CFS score and mortality was reported. The retrospective data from our study was collected from several countries and contains data from more patients and hospitals than in previous studies. The results showed that a higher score on the CFS was associated with a higher risk of hospital mortality in adults of all ages with COVID-19. Furthermore, the data in our study supported the use of CFS scores in patients younger than 65 years with COVID-19. Taken together, the results from the larger prospective study by Hewitt and colleagues[8] and our large retrospective study suggest that CFS score is positively associated with mortality in patients with COVID-19.

With respect to the secondary outcome in our study, analysis of the total sample showed that frail patients had a higher risk of admission to intensive care during the COVID-19 hospitalisation than fit patients ($CFS_{6–9}$ *vs* $CFS_{1–3}$), whereas mildly frail patients had a lower risk of an admission to intensive care than fit patients ($CFS_{4–5}$ *vs* $CFS_{1–3}$). For patients younger than 65 years, there was a significantly higher incidence of admission to intensive care for frail patients compared with fit patients, whereas there was no significant difference in the incidence of admission to intensive care between mildly frail patients and fit patients. For patients aged 65 years and older, there was no significant difference in the incidence of admission to intensive care between frail patients and fit patients; however, the incidence of admission to intensive care was significantly lower in mildly frail patients than in fit patients.

In the present study no data were collected on disease-course severity, the occurrence of a cardiovascular event, or the time from COVID-19 symptom onset to death. If such data had been available, they would have contributed to the understanding of the mixed results with respect to admission to intensive care. There might be several possible explanations for these mixed results. A decision to admit a patient to intensive care is difficult, complex, and highly contingent on context. Such decisions are dependent on the limited resources available in the COVID-19 pandemic,[23] a priori intensive care unit admission criteria, and patient wishes. Treating physicians could decide to refrain from admission to intensive care in frail, older patients because it might be considered that these patients should only be admitted to intensive care with predefined, reasonable goals of care. Such considerations vary across hospitals, regions, and countries,[24] and might explain why

frail patients aged 65 years and older do not have a significantly higher risk of an admission to intensive care. However, this is an assumption because we do not have data on why patients were admitted or not to intensive care.

Another possible explanation might be that patients aged 65 years and older who are mildly frail have a higher prevalence of cardiovascular diseases (27%) compared with fit patients (22%) and frail patients (24%; table 2). It is known that in patients with COVID-19, cardiovascular disease is closely related to a severe course of the infection.[25,26] The CFS focuses on physical impairments, which in the case of underlying cardiovascular disease, might be inadequate. A severe atherosclerotic cardiovascular disease might not translate into a high CFS score but might have led to sudden deterioration or death due to a cardiovascular event before an admission to intensive care could take place.

Our results support the finding that CFS score might also be a suitable marker for hospital mortality in patients younger than 65 years, as was shown in a COVID-19 study,[8] and two non-COVID-19 studies.[15,16] However, the concept of frailty should be applied with caution to younger patients. The understanding of living a life with disability cannot necessarily be extended to disability that is acquired as a manifestation of age-related frailty (Rockwood K, Dalhousie University, personal communication). Because of the scarcity of scientific evidence for the use of the CFS in patients younger than 65 years, critical clinical decisions should not be solely based on the CFS score in these patients. Our data indicate that frail patients younger than 65 years had a higher rate of admission to intensive care than frail patients aged 65 years and older. This might indicate that patients younger than 65 years were not withheld from admission to intensive care based on solely their CFS score. However, we did not collect data on refraining from admission to intensive care. Before applying the CFS to patients younger than 65 years, a greater understanding of the implications of a frail phenotype across different ages, and in a range of long-term conditions, is required.[27,28]

This study has several strengths. First, patients with COVID-19 were included from 63 hospitals in 11 European countries, including both academic and non-academic hospitals. Second, data were collected and critically reviewed by experts, such as clinical pharmacologists, pharmacists, and treating physicians. Finally, the protocol was published for scientific transparency.[20]

This study also had several limitations. The first potential limitation was associated with the data collection during a very demanding period for health-care professionals. To generate a representative cohort and facilitate data collection, a pragmatic design was chosen that focused on the primary research question—ie, the association between medication use and clinical outcomes of patients with COVID-19. Taken together, the pragmatic study design and the focus of the research meant that the availability of data for important variables was limited. In particular, no data were collected about the different treatment strategies patients received for their SARS-CoV-2 infection.

Furthermore, although a large total number of centres participated, there were few centres and patients per country. This prohibited the use of more sophisticated statistical techniques (ie, mixed-effects models). Data were collected on hospital mortality only, because this was a pragmatic clinical outcome frequently used in the critical care literature. Another suitable proxy for mortality would have been 30-day or 90-day mortality.

Second, due to the detailed medication data, major comorbidities were inferred and included in the multivariate analysis. Although these are not direct measures of these comorbidities, they were the best available proxies.

Third, the study population was based on patients admitted to clinical wards, which limits the generalisability of the results to patients in a pre-hospital setting. Furthermore, we took hospital mortality as our primary outcome. However, some patients might have been transferred to another hospital and died within a short period of time due to the SARS-CoV-2 infection. However, the data did not allow the inclusion of these patients in the analyses.

Fourth, because CFS score was only available in a small portion of the total patients in the COMET study sample, there might have been selection bias. Patients without CFS scores were older, had more comorbidities, and used more drugs than patients for whom CFS score was known. These differences might result in underestimation of the effect of the CFS.

Fifth, to examine confounding by indication we stratified the total sample for admission to intensive care and analysed the association between CFS score with hospital mortality. These results show that the associations are similar comparing patients with and without an admission to intensive care. However, when also stratifying by age, the subgroups were too small to accurately estimate the OR and 95% CIs.

A final potential limitation concerns information bias. The classification of patients in the CFS categories was completed by the treating physician irrespective of previous experience with scoring CFS. This might have led to some misclassification of patients. However, it is likely that this bias was limited as there are several studies indicating sufficient interrater reliability of the CFS.[29–32] Although there is still some variability in interrater agreement, the CFS is prognostically relevant.[30]

The present study showed an important direction for future research. The mixed results with respect to the association between CFS score and admission to intensive care shows that more research is needed to understand the dynamics. It might be possible to analyse these associations stratified for policies on admission to intensive care.[24] Furthermore, future studies should repeat the present

analysis in larger samples of patients with COVID-19 who are younger than 65 years to validate the CFS as an instrument for critical care triage decisions.

In conclusion, we show that frail patients ($CFS_{6–9}$) of all ages admitted to hospital with COVID-19 had significantly higher hospital mortality than fit patients ($CFS_{1–3}$). These results suggest that CFS score is a suitable risk marker for hospital mortality in patients with COVID-19. However, treatment decisions based on the CFS in patients younger than 65 years should be made with caution.

Contributors

RSGS, ML, WJRR, HvdK, JV, and MCF contributed to the study design, data collection, data analysis, and writing and revision of the article. BPAvdL contributed to the study design, data collection, and revision of the article. EB contributed to the study design, data analysis, and revision of the article. JALvK contributed to the interpretation of data and the writing and revision of the article. HAP-B and SPM contributed to the writing and revision of the article. All other authors in the COMET research team contributed to data collection and revision of the article. RSGS, ML, and WJRR accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The individual, de-identified patient data that underlie the results reported in this Article (text, tables, figures, and appendices) are available on reasonable request from the corresponding author (HvdK; h.vanderkuy@erasmusmc.nl) under certain conditions (with the consent of all participating centres and with a signed data access agreement).

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