


Clinical Frailty Scale for risk stratification in patients with SARS-CoV-2 infection

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ABSTRACT

Predictive factors for adverse outcomes in patients with COVID-19 are urgently needed. Data related to the applicability of the Clinical Frailty Scale (CFS) for risk stratification in patients with COVID-19 are currently lacking. We investigated the ability of CFS to predict need for mechanical ventilation and the duration of hospital stays in European patients with COVID-19. In total, 42 patients with confirmed COVID-19 infection admitted to the University Medical Center Mainz between March 3 and April 15 2020 were included into this validation study and data were retrospectively analyzed. CFS was assessed at admission in all patients. Patients were followed for need for mechanical ventilation and time to hospital discharge. At admission, the median CFS was 3 (range: 1–7) and 14 (33.3%) patients were considered as at least pre-frail (CFS >3). 24 (57.1%) patients were discharged from hospital after a median time of 7 days (IQR 4–8). 12 (28.6%) patients developed acute respiratory distress syndrome and required mechanical ventilation. In multivariable Cox regression analyses, higher CFS scores (HR 1.659, 95% CI 1.090 to 2.525, $p=0.018$) were an independent predictor for a higher risk of mechanical ventilation after adjusting for age, Charlson Comorbidity Index and quick sepsis-related organ failure score. Additionally, lower CFS scores (HR 0.554, 95% CI 0.312 to 0.983, $p=0.043$) were associated with earlier discharge from hospital. In conclusion, this report demonstrates the usefulness of the CFS for risk stratification at hospital admission in patients with COVID-19.

BACKGROUND

COVID-19 as caused by severe acute respiratory syndrome coronavirus 2 infection is a serious health threat and a highly dynamic global pandemic. Data from China indicated that older age is a risk factor for an adverse outcome.¹ However, even younger patients may develop severe acute respiratory distress syndrome (ARDS).² Given the limited amount of health-care resources, it is of pivotal importance to identify predictive factors for adverse outcomes that allow optimal patient management. A well-known predictor for adverse outcomes in chronic as well as acute diseases is the loss of functional reserve, which is called frailty—a syndrome of

decreased reserve and resistance to stressors and a multifactorial construct of a cumulative decline in different physiological systems.^{3 4} In recent years, several studies investigated the impact of frailty on the prognosis in patients with different chronic diseases like liver cirrhosis. Here, the Clinical Frailty Scale (CFS) was introduced as a promising, easy to apply and inexpensive tool to assess and score frailty with comparable predictive ability as more time-consuming testing strategies like the Fried Frailty Criteria or the Short Physical Performance Battery.⁵ In the context of the ongoing COVID-19 pandemic, risk stratification to allow for an optimal use of limited health-care resources is warranted. In particular hard clinical outcomes including the need for mechanical ventilation or death can support clinicians to reach informed treatment decisions.

Data related to the applicability of CFS in patients with COVID-19 are currently lacking. Therefore, we investigated the ability of CFS to predict need for mechanical ventilation and longer hospital stays in European patients with COVID-19.

METHODS

Patients with confirmed COVID-19 infection admitted to the University Medical Center Mainz (Rhineland-Palatinate, Germany) between March 3 and April 15 2020 were included into this validation study and data were retrospectively analyzed. Clinical characteristics, laboratory values and CFS were assessed at admission in all patients. Four patients were transferred to our center from other hospitals. In these cases, clinical characteristics and laboratory values were available from the initial hospital admission. CFS was subsequently assessed at admission in Mainz. Patients were treated on intensive care unit when in need for mechanical ventilation due to ARDS.

Clinical Frailty Scale

CFS is based on clinical assessment and divided into nine categories according to patients' daily functioning: 1: very fit (people who exercise regularly); 2: well (active people without disease symptoms); 3: well with treated comorbid diseases (people with well-controlled medical problems); 4: apparently vulnerable



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(people whose symptoms limit daily activities); 5: mildly frail (people with need for help in daily routine); 6: moderately frail (people with need for help in house activities and, eg, bathing); 7: severely frail (people who are completely dependent for personal care); 8: very severely frail (people who are approaching the end of life); 9: terminally ill (life expectancy <6 months)).^{5,6} A detailed description of the CFS categories is displayed in the publication of Tandon *et al.*⁵ According to accepted definitions, frailty is defined as a CFS >4 and pre-frailty as a CFS >3. In every patient, a physician assessed CFS.

Ethics

The study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki (sixth revision, 2008).

Statistics

Data were analyzed using SPSS Statistics 23.0, GraphPad Prism 8 and R V3.6.1. Quantitative data are expressed as medians with IQRs, and categorical variables are given as frequencies and percentages. Correlations were performed using Spearman's rank correlation. For univariable and multivariable analyses, Cox regression models were conducted. Harrell's C-index was used to evaluate the discriminative performance of these Cox models. In addition, the calibration of a univariable Cox regression model with CFS as the only covariate was evaluated for different time points by using the pec package in R.

Time to hospital discharge for pre-frail (CFS>3) and not pre-frail patients was analyzed using a cumulative incidence plot. The endpoints of the study were need for mechanical ventilation and days until discharge from hospital. The time to hospital discharge was counted from the time point of admission at any hospital.

Our complete data analysis is exploratory. Hence, no adjustments for multiple testing were performed. For all tests, we used a 0.05 level to define statistically relevant deviations from the respective null hypothesis.

RESULTS

Clinical characteristics of the study cohort at admission

A total of 42 patients with a median age of 67.5 (IQR 54.5–75.25) years were recruited (males: 75%). At admission, median Charlson Comorbidity Index (CCI) was 3 (IQR 1–5) and the median CFS was 3 (range: 1–7). Fourteen (33.3%) patients were considered as at least pre-frail (CFS >3) and 6 (14.3%) as frail (CFS >4). The most common symptoms at hospital admission were cough (71%) followed by fever (69%) and dyspnea (60%). Gastrointestinal symptoms were only present in 14% of the patients. There was a positive correlation between CFS and CCI ($r=0.694$, $p<0.001$) or quick sepsis-related organ failure score (qSOFA) ($r=0.412$, $p=0.007$) at admission.

Other baseline characteristics of the cohort at hospital admission are displayed in [table 1](#).

CFS for the prediction of need for mechanical ventilation and days until discharge from hospital

Twenty-four (57.1%) patients were discharged from hospital after a median time of 7 (IQR 4–8) days. The other patients were still treated in hospital at the end of

follow-up or deceased ($n=2$). Twelve (28.6%) patients developed an ARDS and required mechanical ventilation. Two patients died during the observation period (both CFS 4). In univariable Cox regression analyses, there was a clear trend between higher CFS scores and need for mechanical ventilation during follow-up (HR 1.361, 95% CI 0.998 to 1.857, $p=0.052$; C-index 0.722), while there was a significant association between lower CFS scores and earlier discharge from hospital (HR 0.531, 95% CI 0.354 to 0.797, $p=0.002$; C-index 0.742). Calibration curves for these univariable Cox models for both endpoints are displayed in online supplementary figures 1 and 2. Patients with a CFS <3 were earlier and more frequently discharged from hospital compared with at least pre-frail patients (CFS ≥ 3) ([figure 1](#)). In multivariable Cox regression analyses, higher CFS scores (HR 1.659 per CFS level, 95% CI 1.090 to 2.525, $p=0.018$) were an independent predictor for a higher risk of mechanical ventilation after adjusting for age (HR 0.947, 95% CI 0.890 to 1.009, $p=0.091$), CCI (HR 0.991, 95% CI 0.688 to 1.428, $p=0.962$) and qSOFA (HR 5.590, 95% CI 1.946 to 16.060, $p=0.001$). Additionally, lower CFS scores (HR 0.554, 95% CI 0.312 to 0.983, $p=0.043$) were associated with earlier discharge from hospital after adjusting for age (HR 1.023, 95% CI 0.980 to 1.068, $p=0.305$), CCI (HR 0.877, 95% CI 0.667 to 1.152, $p=0.345$) and qSOFA (HR 0.713, 95% CI 0.329 to 1.544, $p=0.391$).

In a further step, we evaluated the usefulness of a combination of CFS, leukocytes or C reactive protein (CRP). A model containing CFS and CRP showed the best discriminative performance (C-index 0.851) to predict the endpoint of hospital discharge, while a combination of CFS, leukocytes and CRP was best to predict the need for mechanical ventilation (C-index 0.873).

DISCUSSION

This is the first report to demonstrate the usefulness of the CFS for risk stratification at hospital admission in patients with COVID-19. We could show that there is a strong positive correlation between higher CFS scores and need for mechanical ventilation or the length of hospital stays independent of age, comorbidities and qSOFA at admission. These findings are of pivotal importance, as the CFS is an easy to use tool and allows prognostic stratification of patients with COVID-19 at the time of initial hospitalization. These measures could allow providers to better use healthcare resources at time where these are urgently needed.

The usefulness of CFS is not surprising, as its ability to predict adverse outcomes in different chronic diseases has been previously shown.⁵ Additionally, studies conducted by Fernando *et al* demonstrated in large cohorts that the presence of frailty (CFS >4) is associated with an increased mortality in elderly patients with infections and extubation failure, need for tracheostomy and higher in-hospital mortality in patients with need for invasive mechanical ventilation.^{7,8}

While it appears to be obvious that the prognosis of patients infected with COVID-19 is determined by age and the presence of comorbidities, our data support the assumption that the physical reserve as determined by CFS may be an additional important and even stronger determinant for

Table 1 Characteristics of the entire cohort at hospital admission

| Variables | Total cohort | Patients with need for mechanical ventilation during follow-up | Patients treated on normal wards |
|---------------------------------------|-------------------|--|----------------------------------|
| n | 42 | 12 (29) | 30 (71) |
| Age (years) | 67.5 (54.5–75.25) | 70.5 (54–74) | 65.5 (56–76) |
| Male gender | 29 (69) | 9 (75) | 20 (67) |
| CFS | 3 (2–4) | 3.5 (3–4) | 2 (2–4) |
| CFS >3 | 14 (33) | 6 (50) | 8 (27) |
| qSOFA | 0 (0–1) | 1 (1–2) | 0 (0–1) |
| Symptoms at admission | | | |
| Cough | 30 (71) | 8 (67) | 22 (73) |
| Fever | 29 (69) | 8 (67) | 21 (70) |
| Dyspnea | 25 (60) | 10 (83) | 15 (50) |
| Gastrointestinal symptoms | 6 (14) | 2 (17) | 4 (13) |
| Comorbidities | | | |
| CCI | 3 (1–5) | 3.5 (1–5) | 3 (1–5) |
| Diabetes mellitus | 8 (19) | 3 (25) | 5 (17) |
| Arterial hypertension | 19 (45) | 5 (42) | 14 (47) |
| Chronic obstructive pulmonary disease | 6 (14) | 1 (8) | 5 (17) |
| Cancer | 4 (10) | 1 (8) | 3 (10) |
| Laboratory values at admission | | | |
| Sodium (mmol/L) | 138 (134–140) | 139 (133–141) | 138 (134–139) |
| Creatinine (mg/dL) | 1.0 (0.7–1.4) | 1.2 (1.0–1.9) | 0.9 (0.7–1.3) |
| CRP (mg/L) | 101 (31–198) | 263 (173–305) | 55 (16–132) |
| Procalcitonin (ng/mL) | 0.12 (0.03–0.24) | 0.33 (0.19–2.03) | 0.05 (0.02–1.28) |
| Total bilirubin (g/dL) | 0.7 (0.5–0.9) | 0.8 (0.7–1.4) | 0.6 (0.4–0.9) |
| AST (U/L) | 47 (29–74) | 69 (51–120) | 41 (28–60) |
| ALT (U/L) | 27 (15–43) | 33 (20–54) | 25 (15–43) |
| INR | 1.1 (1.1–1.2) | 1.2 (1.1–1.3) | 1.1 (1.1–1.2) |
| Leukocytes (10 ⁹ /L) | 6.9 (4.7–8.9) | 8.8 (4.4–10.2) | 6.1 (4.8–7.6) |
| Hemoglobin (g/L) | 134 (121–146) | 130 (117–151) | 137 (122–144) |
| Thrombocytes (10 ⁹ /L) | 205 (151–271) | 315 (171–206) | 205 (133–256) |
| CK (U/L) | 128 (54–390) | 247 (54–810) | 97 (54–310) |
| LDH (U/L) | 395 (295–530) | 496 (452–547) | 331 (258–525) |
| D-dimer (mg/L)* | 1.2 (0.6–3.5) | 2.0 (0.8–2.6) | 1.0 (0.45–3.5) |
| Course/outcome | | | |
| Discharged | 24 (57) | 2 (17) | 22 (73) |
| Time until hospital discharge (days) | 7 (4–8) | 16 (14–18) | 6.5 (4–8) |
| Deceased | 2 (5) | 2 (17) | 0 (0) |

Data are expressed as median with IQRs or as frequencies with percentages.

*Measured in 35 patients.

ALT, alanine aminotransaminase; AST, aspartate aminotransferase; CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale; CK, creatine kinase; CRP, C reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; qSOFA, quick sepsis-related organ failure score.

adverse outcomes. Additionally, our results underline the fact that it may not be simply the number of age that determines a more severe course of the COVID-19 infection but rather the reduced physiological reserve prior to hospitalization. Taken together, CFS may add another dimension for risk stratification in patients with COVID-19 and could be useful not only to guide decision-making of clinicians but also for goals-of-care decisions with patients and their caregivers.

The characteristics of our cohort are in line with a previously published report from another city in Germany, while European cohorts seem to differ significantly from Chinese patients with COVID-19.^{2,9} Those appear to be younger and have a lower frequency of comorbidities than European patients.

Our study has several limitations that have to be acknowledged. First, we report data of a relatively small number of patients from a single center. Although especially the number of outcomes like need for mechanical ventilation are quite small, we were able to demonstrate a robust association between CFS and adverse outcomes. Though, it has to be mentioned that our models are prone to overfitting and effect estimates should be interpreted in combination with their respective 95% CIs. Furthermore, characteristics between European cohorts and especially Chinese patients differ significantly. Therefore, our results may only be generalizable for the western world and should be interpreted with caution for risk prediction in Chinese patients.

In conclusion, our data support the usefulness of CFS as an easy additive tool for risk stratification of patients with

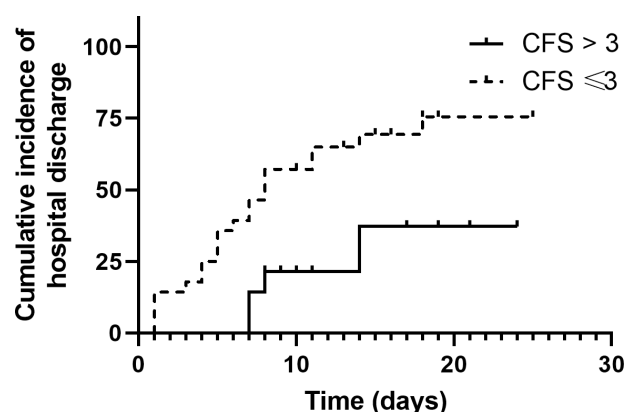


Figure 1 Impact of pre-frailty (Clinical Frailty Scale (CFS) >3) on time to discharge from the hospital ($p=0.014$).

COVID-19 at admission independently of comorbidities, age or qSOFA. Thus, regular testing with the CFS at hospital admission may identify patients at higher risk for worse disease progression and finally lead to an improvement of care in patients with COVID-19. Future prospective multi-center studies are needed to validate these findings.

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