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Prevalence of New Frailty at Hospital Discharge in Severe COVID-19 Survivors and Its Associated Factors

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Abstract

Background: The development of frailty at hospital discharge affects the clinical outcomes in severe coronavirus disease 2019 (COVID-19) survivors who had no frailty before hospitalization. We aimed to describe the prevalence of new frailty using the clinical frailty scale (CFS) and evaluate its associated factors in patients with severe COVID-19 without pre-existing frailty before hospitalization.

Methods: We performed a secondary analysis of clinical data from a nationwide retrospective cohort collected from 22 hospitals between January 1, 2020 and August 31, 2021. The patients were at least 19 years old and survived until discharge after admission to the intensive care unit (ICU) because of severe COVID-19. Development of new frailty was defined as a CFS score ≥5 at hospital discharge.

Results: Among 669 severe COVID-19 survivors without pre-existing frailty admitted to the ICU, the mean age was 65.2±12.8 years, 62.5% were male, and 50.2% received mechanical ventilation (MV). The mean CFS score at admission was 2.4±0.9, and new frailty developed in 27.8% (186/483). In multivariate analysis, older age, cardiovascular disease, CFS score of 3–4 before hospitalization, increased C-reactive protein level, longer duration of corticosteroid treatment, and use of MV and extracorporeal membrane oxygenation were identified as factors associated with new-onset frailty.

Conclusion: Our study suggests that new frailty is not uncommon and is associated with diverse factors in survivors of severe COVID-19 without pre-existing frailty.

Keywords: Severe COVID-19; Frailty; Clinical Frailty Scale; Intensive Care Unit

Introduction

Frailty is a clinical state of increased vulnerability to stressful event, which is caused by multicomplex functional decline of cognitive, physical, and/or physiologic reserves[1]. Frailty is commonly seen in critically ill patients admitted to intensive care unit (ICU)[2], as critical illness leads to the development and progression of frailty[3,4]. Frailty has been recognized as a common risk factor associated with poor clinical outcomes in critically ill patients[2,5,6], leading to growing concern about frailtty[7]. Therefore, thoroughly assessing frailty in crit-

ically ill patients in the ICU using feasible and reliable tools is crucial[8]. The clinical frailty scale (CFS) is a validated and reliable tool to evaluate frailty[9-11], CFS-guided frailty assessment is reportedly associated with worse outcomes in critically ill patients[6,12-15].

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has imposed a global health burden. COVID-19 patients with severe and critical conditions require admission to the ICU due to numerous complications involving various organs, which has led to high morbidity and mortality[16-20]. Numerous factors, including frailty, are reportedly associated with poor outcomes in critically ill patients with COVID-19[16-18,21]. Moreover, frailty is associated with worse clinical outcomes in critically ill patients with COVID-19 than in those without COVID-19 admitted to the ICU[22].

The development of frailty at hospital discharge in critically ill COVID-19 patients who were non-frail before hospitalization had a significant influence on long-term clinical outcomes. However, there is limited awareness of the prevalence and characteristics of new-onset frailty at hospital discharge, and this has not been well addressed.

Therefore, the aim of study was to describe the prevalence of new frailty, as assessed using the CFS, and evaluate its associated factors in severe COVID-19 survivors without pre-existing frailty before hospitalization using a nationwide multicenter cohort of South Korea.

Table 1. Comparison of baseline, clinical characteristics and therapeutic modality between critically ill patients with frailty and those without frailty at the time of hospital discharge

Variable	Total (n=669)	Frailty (n=186)	Non-frailty (n=483)	p-value
Age, yr-old	63.5±12.8	68.4±11.1	61.7±12.9	<0.001
Male sex	418 (62.5)	110 (59.1)	308 (63.8)	0.268
BMI, kg/m^2	25.2±3.9	25.0±3.8	25.2±3.9	0.465
Comorbidities	448 (67)	151 (81.2)	297 (61.5)	<0.001
Hypertension	325 (48.6)	107 (57.5)	218 (45.1)	0.004
Diabetes mellitus	207 (30.9)	75 (40.3)	132 (27.3)	0.001
Cardiovascular disease	53 (7.9)	28 (15.1)	25 (5.2)	<0.001
Chronic lung disease	38 (5.7)	13 (7)	25 (5.2)	0.364
Chronic liver disease	14 (2.1)	8 (4.3)	6 (1.2)	0.029
Chronic kidney disease	28 (4.2)	15 (8.1)	13 (2.7)	0.002
Chronic neurologic disease	34 (5.1)	15 (8.1)	19 (3.9)	0.029
Solid tumor	31 (4.6)	12 (6.5)	19 (3.9)	0.165
CFS before admission	2.4±0.9	2.8±1.0	2.3±0.9	<0.001
CFS 1–2	333 (49.8)	58 (31.2)	275 (56.9)	<0.001
CFS 3–4	336 (50.2)	128 (68.8)	208 (43.1)	
SOFA score	5.1±3.2	6.9±3.4	4.4±2.8	<0.001
Use of remdesivir	499 (74.6)	142 (76.3)	357 (73.9)	0.518
Corticosteroid	634 (94.8)	180 (96.8)	454 (94)	0.148
Tocilizumab	70 (10.5)	21 (11.3)	49 (10.1)	0.665
RRT	23 (3.4)	15 (8.1)	8 (1.7)	<0.001
Use of HFNO	567 (84.8)	137 (73.7)	430 (89)	<0.001
Use of MV	336 (50.2)	144 (77.4)	192 (39.8)	<0.001
Prone position	122 (18.2)	67 (36)	55 (11.4)	<0.001
ECMO	51 (7.6)	30 (16.1)	21 (4.3)	<0.001

Values are presented as mean±standard deviation or number (%).
BMI: body mass index; CFS: clinical frailty score; SOFA: sequential organ failure assessment; RRT: renal replacement therapy; HFNO: high-flow nasal oxygen therapy; MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation.

Materials and Methods

1. Patients

We performed a secondary analysis of the clinical data of patients with severe COVID-19 in a nationwide, multicenter, retrospective cohort collected from 22 tertiary- or university-affiliated hospitals between January 1, 2020 and August 31, 2021. The patients were at least 19 years old who had clinical symptoms, signs, and radiological features consistent with COVID-19 and positive polymerase chain reaction test for SARS-CoV-2. Patients without pre-existing frailty before hospitalization who were admitted to the ICU because of the requirement of high-flow oxygen therapy were selected from this cohort for this analysis, and survivors at hospital discharge were included.

This study was approved by the Institutional Review Board (IRB) of the Gyeongsang National University Hospital (IRB number 2021-012-020) and local committees of all other participating centers. The requirement for informed consent was waived owing to the retrospective nature of the study.

2. Data collection

The collected patient characteristics included age, sex, body mass index, comorbidities, frailty, and sequential organ failure assessment (SOFA). Data regarding laboratory parameters, medical treatments, and oxygen therapy modalities were also collected. In addition to oxygen therapy modality, information on rescue therapy, such as the use of renal replacement therapy, prone positioning, and extracorporeal membrane oxygenation (ECMO), was collected. Outcome data, such as length of stay in the ICU and/or hospital and ICU mortality, were also included. The CFS was used as a tool to evaluate frailty[9]; a CFS score ≥5 was at the time of hospital discharge defined as frailty[15].

3. Statistical analysis

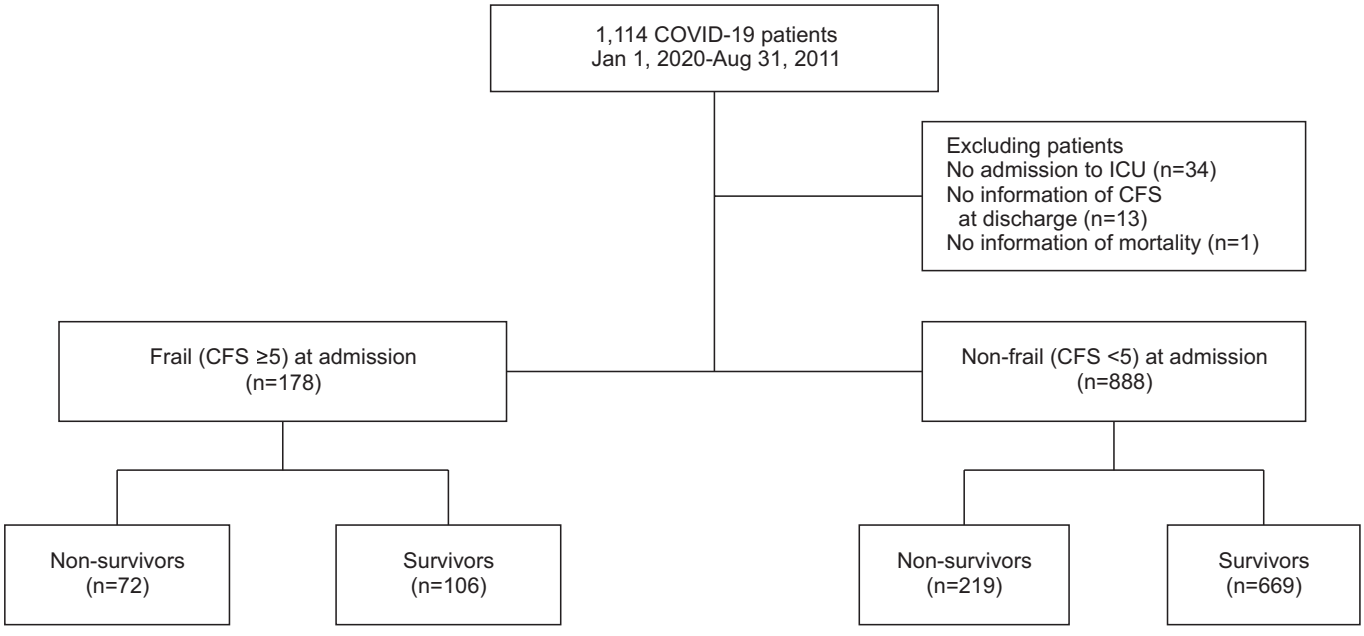
Non-continuous variables are expressed as numbers (%) and were compared using the chi-square test or Fisher's exact test, whereas continuous variables are expressed as the mean±standard deviation and were compared using the Student's t-test or Mann-Whitney U test. Univariate and multivariate logistic regression analyses were performed to identify factors associated with frailty. All data were analyzed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA), and p-values <0.05 indicated statistical significance.

Results

1. Patients' characteristics and therapeutic modalities

The clinical data of 669 frail, severe COVID-19 survivors without pre-existing frailty before hospitalization were analyzed (Table 1 and Figure 1). The mean age of all included patients was 63.5±12.8 years, among

Figure 1. Flow of the study patients' enrollment. COVID-19: coronavirus disease 2019; ICU: intensive care unit; CFS: clinical frailty scale.



whom 62.5% were male. Approximately two-thirds of the patients had at least one comorbidity. Before hospitalization, 137 (20.5%), 196 (29.3%), 254 (38%), and 82 patients (12.3%) had CFS scores of 1, 2, 3, and 4, respectively. The prevalence of frailty (CFS score ≥5) was 27.8% (186/483). The prevalence of frailty was significantly higher in patients with a higher pre-hospital CFS score (16.8% in patients with a CFS score of 1; 17.9% in CFS 2; 30.7% in CFS 3; and 61% in CFS 4; p<0.001). Compared with patients without frailty, a significantly higher proportion of patients with frailty at discharge had CFS scores of 3–4 before admission (68.8% vs. 43.1%, p<0.001). Patients with frailty were older and had more comorbidities and higher SOFA scores than those without frailty. Regarding therapeutic interventions during hospitalization, a significantly higher proportion of patients with frailty received renal replacement therapy, mechanical ventilation, prone positioning, and ECMO.

2. Comparison of laboratory and duration parameters

The laboratory and duration parameters are presented in Table 2. Patients with frailty had lower hemoglobin and albumin levels and higher blood urea nitrogen, lactate dehydrogenase, C-reactive protein (CRP), and D-dimer levels than those without frailty. The duration of corticosteroid administration (34.7±42.2 days vs. 18.0±16.3 days) and use of mechanical ventilation (30.4±30.6 days vs. 14.7±27.9 days) were significantly longer in patients with frailty (p<0.00). The length of stay in the ICU (32.0±28.5 vs. 15.6±19.5) and hospital (54.9±48.1 vs. 24.3±24.8) were also significantly longer in patients with frailty than in those without frailty (p<0.001).

3. Analysis of factors associated with development of frailty in critically ill COVID-19 patients without pre-existing frailty before hospitalization

As shown in Table 3, among variables with p-values <0.05 entered into univariate analysis, older age (odds ratio [OR], 1.040; 95% confidence interval [CI], 1.020 to 1.061; p<0.001), cardiovascular disease (OR, 2.746; 95% CI, 1.382 to 5.454; p=0.004), CFS score of 3–4 before admission (vs. CFS score of 1–2: OR, 2.194; 95% CI, 1.394 to 3.452; p=0.001), increased CRP levels (OR, 1.006; 95% CI, 1.002 to 1.011; p=0.006), duration of corticosteroid administration (OR, 1.010; 95% CI, 1.001 to 1.019; p=0.006), receiving mechanical ventilation (OR, 2.225; 95% CI, 1.247 to 3.972; p=0.007), receiving ECMO (OR, 2.908; 95% CI, 1.261 to 6.706; p=0.012), and longer ICU stay (OR, 1.014; 95% CI, 1.000 to 1.027; p=0.042) were significantly associated with the development of frailty in severe COVID-19 patients who survived to discharge.

Table 2. Comparison of laboratory and several duration parameters between critically ill patients with frailty and those without frailty at the time of hospital discharge

Variable	Total (n=669)	Frailty (n=186)	Non-frailty (n=483)	p-value
WBC, $\times10^3/mm^3$	8.4±4.9	9.4±6.9	8.1±3.9	0.129
Hemoglobin, g/dL	13.3±2.0	13.0±2.3	13.4± 1.9	0.024
Platelet, $\times10^3/mm^3$	205.3±79.2	196.8±75.9	208.5±80.3	0.119
BUN, mg/dL	20.2±13.0	23.3±14.6	19.0±12.2	<0.001
Creatinine, mg/dL	0.9±0.9	1.1±1.3	0.9±0.6	0.179
Albumin, g/dL	3.3±0.6	3.2±0.5	3.4±0.5	<0.001
LDH, U/L	528.8±277.7	593.5±393	501.9±207.1	0.003
CRP, mg/dL	22.9±43.2	31.6±55.6	19.5±36.8	0.038
D-dimer	3.1±6.4	4.5±7.1	2.5±5.9	<0.001
Duration of corticosteroid administration, day	22.6±27.2	34.7±42.2	18.0±16.3	<0.001
Duration of MV, day	21.4±30.1	30.4±30.6	14.7±27.9	<0.001
LOS of ICU, day	20.2±23.5	32.0±28.5	15.6±19.5	<0.001
LOS of hospital, day	32.8±35.7	54.9±48.1	24.3±24.8	<0.001

Values are presented as mean±standard deviation.
WBC: white blood cell; BUN: blood urea nitrogen; LDH: lactate hydrogenase; CRP: C-reactive protein; MV: mechanical ventilation; LOS: length of stay; ICU: intensive care unit.

Table 3. Univariate and multivariate analyses for factors associated with new frailty at hospital discharge in critically ill and non-frail patients with COVID-19 who survived

Variable	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.047	1.031–1.064	<0.001	1.040	1.020–1.061	<0.001
Male sex	0.822	0.582–1.163	0.268			
BMI	0.986	0.944–1.030	0.523			
Hypertension	1.646	1.170–1.646	0.004			
Diabetes mellitus	1.797	1.260–2.562	0.001			
Cardiovascular disease	3.247	1.838–5.734	<0.001	2.746	1.382–5.454	0.004
Chronic lung disease	1.377	0.689–2.752	0.366			
Chronic liver disease	3.573	1.223–10.442	0.020			
Chronic kidney disease	3.171	1.479–6.802	0.003			
Chronic neurologic disease	2.142	1.065–4.311	0.033			
Solid tumor	1.684	0.801–3.542	0.169			
CFS 3–4 (vs. 1–2) before admission	2.918	2.038–4.177	<0.001	2.194	1.394–3.452	0.001
SOFA at admission	1.276	1.206–1.349	<0.001	1.079	0.994–1.172	0.068
WBC	1.053	1.018–1.090	0.003			
Hemoglobin	0.900	0.825–0.982	0.018			
PLT	0.998	0.996–1.000	0.088			
BUN	1.024	1.010–1.037	<0.001			
Creatinine	1.412	1.139–1.746	0.002			
Albumin	0.444	0.315–0.627	<0.001			
CRP	1.006	1.002–1.009	0.002	1.006	1.002–1.011	0.006
Use of remdesivir	1.139	0.768–1.690	0.518			
Use of corticosteroid	1.916	0.782–4.694	0.155			
Duration of corticosteroid use	1.026	1.017–1.035	<0.001	1.010	1.001–1.019	0.031
Use of MV	5.196	3.522–7.668	<0.001	2.225	1.247–3.972	0.007
Use of ECMO	4.231	2.354–7.605	<0.001	2.908	1.261–6.706	0.012
LOS, ICU	1.038	1.028–1.048	<0.001	1.014	1.000–1.027	0.042

Forward stepwise method was used for analysis.
COVID-19: coronavirus disease 2019; OR: odds ratio; CI: confidence interval; BMI: body mass index; CFS: clinical frailty scale; SOFA: sequential organ failure assessment; WBC: white blood cell; PLT: platelet count; BUN: blood urea nitrogen; CRP: C-reactive protein; MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation; LOS: length of stay; ICU: intensive care unit.

Discussion

In this study, we described the prevalence of new frailty and evaluate its associated factors in severe COVID-19 survivors without pre-existing frailty before hospitalization. We found that frailty developed at hospital discharge in approximately one-fourth of severe COVID-19 survivors without pre-existing frailty before hospitalization. Even among patients without frailty, defined as having a CFS score ≤4, frailty developed more frequently in patients with a CFS score of 3–4 (vulnerable) than those with a score of 1–2 (fit). The lengths of ICU and hospital stays were significantly longer in survivors with frailty than in those without. Older age, cardiovascular disease, pre-hospital CFS score of 3–4, higher CRP level, longer duration of corticosteroid administration, mechanical ventilation use, ECMO use, and longer stay in the ICU were factors associated with new frailty.

Frailty is a clinical syndrome that occurs as a result

of various diseases and medical conditions. It reflects a single or combined functional decline ranging from physical, physiologic, to cognitive reserves, leading to increased individual vulnerability to stressful events[1]. Critical illness leads to frailty or *vice versa*[3,6]; notably, frailty is commonly seen in critically ill patients admitted to the ICU and has been recognized as a risk factor associated with poor clinical outcomes in critically ill patients[2,5,13,23].

The COVID-19 pandemic, caused by SARS-CoV-2, poses a significant threat to global health. Among several clinical manifestations of COVID-19, severe and/or critical conditions such as respiratory failure were attributable to increased admission to the ICU and higher mortality[17,19]. Several large cohort studies have addressed numerous factors associated with poor outcomes in critically ill patients with COVID-19[16,21]. Among these, frailty has drawn attention as one of the important risk factors for poor prognosis in patients with COVID-19[24]. Frailty is associated with worse clinical outcomes in critically ill patients with COVID-19 as well as in those without critical illness. From this perspective, it is crucial to thoroughly evaluate and implement multidisciplinary approaches for frailty in critically ill patients with COVID-19 admitted to the ICU. Several COVID-19 cohort studies have reported that pre-admission frailty is significantly associated with poor clinical outcomes[25,26]. However, not only pre-admission frailty but also new frailty during hospitalization or at survival to discharge plays a crucial role in the prognosis of critically ill patients with COVID-19. In our study, approximately one-fourth of critically ill COVID-19 survivors without pre-existing frailty developed new frailty at hospital discharge. This prevalence of frailty is unignorable because it may affect late clinical outcomes in critically ill patients[5,27-29].

In our study, several risk factors associated with frailty were identified, most of which were consistent with previous findings[30,31]. In our study, patients in a vulnerable (CFS score of 3–4) condition before admission were more likely to develop frailty at discharge than those who were considered to be in fit (CFS score of 1–2). This finding suggests that a more elaborate evaluation to discriminate between fit and vulnerable statuses is needed and that the CFS may be a useful tool. For patients with cardiovascular disease as an underlying condition, the OR for frailty occurrence increases as much as in cases where ECMO was applied. Close monitoring of development of frailty in patients with cardiovascular disease suggests to be needed.

In addition, a higher CRP concentration was associated with frailty, which reflects inflammation as one of the contributing factors for frailty[32]. Corticosteroids have anti-inflammatory effects, and dexamethasone demonstrated a beneficial effect of reduced mortality in hospitalized COVID-19 patients requiring oxygen supplementation[33]. However, continuous use of corticosteroids inevitably results in multiple adverse effects, including weakness or myopathy[34,35]. In critically ill patients, corticosteroid use has been associated with ICU-acquired weakness, which affects frailty[4,36]. Considering the risk of frailty in critically ill patients with COVID-19, corticosteroids should be used with caution.

Elevated CRP levels is related to the severity of inflammation in COVID-19 patients. Inflammation itself is linked to muscle weakness and muscle loss, which are key contributors to the development of frailty. In the treatment of COVID-19, corticosteroids, one of anti-inflammatory agents, play a critical role in reducing inflammation and improving clinical outcomes, especially in patients requiring supplemental oxygen. However, steroid therapy is not without its risks of adverse effects, such as an increased susceptibility to infections and muscle atrophy, which can exacerbate frailty. In severe cases of COVID-19, both elevated CRP levels and steroid use, while necessary for controlling inflammation, may have detrimental effects on frailty. Therefore, managing inflammation in these patients must be balanced against the potential for these adverse outcomes to prevent development and progression of frailty.

Oxygen supports such as mechanical ventilation and ECMO were associated with increased frailty, which reflects the severity of illness, and their maintenance results in complications such as frailty[20]. Taken together, comprehensive evaluation of a broad range of elements associated with the development of frailty and a multidisciplinary approach to reverse them need to be performed[37].

Our study had some limitations. First, selection bias cannot be excluded because of the retrospective cohort design; however, the collection of data from a large number of patients from a nationwide multicenter study added clinical significance to our results. Second, most patients were included during the early pandemic period in South Korea; therefore, the effects of SARS-CoV-2 variants on frailty could not be explored. Third, because the data collection ended at the time of hospital discharge, the trajectory of new frailty could not be evaluated in terms of the association between the trajectory of frailty and outcomes[38]. Fourth, clinical data of current studies were collected until hospital discharge; thus, the impact of new frailty on long-term

outcomes in ICU survivors could not be determined. Further studies focusing on this aspect are required. Finally, ICU rehabilitation to prevent frailty during ICU admission was not performed at each hospital in our cohort.

In conclusion, new frailty at hospital discharge, as assessed using the CFS, developed in approximately one-fourth of severe COVID-19 survivors without pre-existing frailty before hospitalization. Several factors associated with frailty that can be modified during patient care have been identified. Therefore, routine screening for frailty and multidimensional efforts to reverse potentially modifiable factors may improve the clinical outcomes in survivors of severe COVID-19.

Authors' Contributions

Conceptualization: Jeong JH, Heo M, Yoo JW. Methodology: Jeong JH, Heo M, Yoo JW. Formal analysis: Jeong JH, Heo M, Yoo JW. Data curation: Park S, Lee SH, Park O, Kim T, Yeo HJ, Jang JH, Cho WH, Yoo JW. Validation: Park S, Lee SH, Kim T, Yeo HJ, Jang JH, Cho WH, Yoo JW. Investigation: Park S, Lee SH, Kim T, Yeo HJ, Jang JH, Cho WH, Yoo JW. Writing - original draft preparation: JH Jeong, Heo M, Yoo JW. Writing - review and editing: Yoo JW. Approval of final manuscript: all authors

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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