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Original Article

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Prognostic Evaluation of Frailty Index in Hospitalized Moderate to Severe COVID 19 Geriatric Patients

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ABSTRACT

Background: Elderly people are particularly affected by COVID -19. Elderly people who suffered from other diseases and were frail were particularly likely to develop severe COVID -19 or die from the infection. The aim of the current study is to assess the frailty index in COVID -19 geriatric patients admitted to hospital using the Clinical Frailty Scale and the FI -Lab21 and to establish a relationship between frailty and outcome prediction.

Methods: In a prospective observational study we conducted, we assessed the clinical presentation and frailty-related characteristics of hospitalised individuals aged > 65 years with positive moderate-severe COVID -19 pneumonia. The Clinical Frailty Scale (CFS) and FI Lab-21 criteria were used to assess frailty at the time of admission. Mortality and change in CFS score from admission to discharge were recorded.

Results: The age of patients participating in the study COVID -19 ranged from 65 to 90 years, and the mean age was 72.14±6.13 years. Men predominated in the study population (73.0%). Using the Clinical Frailty Scale (CFS), 21.0% of patients were not frail (score 1-3), 46.0% were mildly to moderately frail (score 5-6), and 33.0% were severely frail (score 7-8). Among the frail patients, the severely frail cases (based on CFS) were significantly older than the mild-to-moderate and nonfrail COVID -19 cases. The mortality rate was significantly higher in severely frail (66.7%) and mild-to-moderately frail (45.7%) patients than in nonfrail (28.6%) patients.

Conclusion: The results show that the clinical frailty scale has no significant association with FILab-21 in COVID -19 cases. CFS showed a significant association with disease progression in COVID -19 cases.

Key Words: *COVID-19, Frailty, Aged, Geriatrics, mortality, Clinical Frailty Scale*

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INTRODUCTION

A new coronavirus (COVID -19) that emerged from SARS-CoV-2 first appeared in Hubei Province, China, in December 2019. It spread rapidly throughout the world, and on March 11, 2020, it was declared a global epidemic by WHO [1]. COVID -19 infection causes respiratory illness and is thought to be transmitted mainly through direct contact with respiratory droplets [2].

All age groups were affected by COVID -19, but the mortality rate was higher in older patients (> 70 years) with or without concomitant diseases [3, 4]. The severity of COVID -19 was higher in the elderly, which may be related to age-related physiological changes [5]. In addition, elderly patients were more prone to various clinical problems such as sarcopenia, cognitive decline, sarcopenia and frailty, which not only aggravate the disease but also accelerate its negative progression [6].

Among the first measures taken by the administration to deal with the crisis were the isolation of accepted persons, the wearing of face masks, the observance of sanitary regulations, the prohibition of public gatherings, and the raising of public awareness. When these measures did not produce the desired results, additional measures were taken, including partial or complete closures, leaving only essential services to be provided. The entire health care system focused exclusively on providing emergency assistance and managing COVID.

The use of the clinical frailty score (CFS) in COVID -19 patients referred to the intensive care unit was recommended by the National Institute for Clinical Excellence (NICE) [7]. Frailty is associated with ageing but can also affect younger adults [8]. The National Health Service Specialist Clinical Frailty Network discourages the use of CFS

alone and emphasises the importance of including clinical discussions in the management of patients, particularly younger or disabled patients for whom CFS has not been validated.

The World Health Organisation describes frailty as "progressive age-related decline in body function, leading to vulnerability and reduced resilience to physical and psychological stressors, and increased risk of adverse health outcomes" [9]. Decreased activity, fatigue, weight loss, sarcopenia, osteopenia, cognitive impairment, and balance problems are signs of frailty [10, 11]. Frailty and chronic diseases are related; the effects of chronic diseases on frailty have been widely documented, and the use of diuretics, antihypertensives, and other medications to treat chronic diseases may also increase frailty [12]. Chronic diseases become more prevalent as the population ages, placing a burden on the health care system and social services [13, 14]. Frail individuals who are hospitalised have to stay longer, are more likely to develop complications there, and have worse outcomes (readmission, referral to an advanced care facility, and mortality) [15].

To identify difficulties, plan for continued medical and social care, and make provisions for special needs, it may be helpful to measure frailty in older patients before admission. Frailty can be measured by a number of different methods, of which the phenotypic approach to frailty [9] and the frailty index [16, 17] are the best known. Recently, the laboratory frailty index (FI -Lab) has been developed based solely on general biochemical/haematological parameters and biomarkers [15, 18]. The aim of the current study is to assess the frailty index using the clinical frailty scale and the FI -Lab21 in COVID -19 geriatric patients admitted to hospitals and to link frailty to outcome prediction.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Medicine, Era's Lucknow Medical University & Hospital (ELMCH). ELMCH is a tertiary care centre with state-of-the-art infrastructure that primarily serves the socioeconomically underprivileged suburban and rural population of Lucknow. All patients with moderate-severe COVID -19 pneumonia aged > 65 years were included. Patients ≤65 years with mild cases of COVID -19 were excluded. The study was approved by the ethical committee of the institution. Informed written consent was obtained from all patients.

A total of 100 patients with moderate-severe COVID -19 pneumonia at > 65 years of age were included in this study. The sample size was calculated based on the prevalence (38%) of clinical frailty score above 6 [19].

All moderate-to-severe COVID -19 patients who met the inclusion criteria were included in the study. Demographic information and clinical findings of the study population were recorded along with laboratory findings. These data were used for analysis. The severity of COVID -19 was determined using the ICMR criteria [20].

Assessment of frailty using the clinical frailty scale

A 9-item scale was used to assess the frailty of patients, with score 1 representing very fit and score 9 representing terminally ill patients, as described by Mendiratta et al. [60] Scores 1-3 on the 9-point scale indicate that patients tend to be fit and doing well; scores 4-6 indicate mild/medium frailty; scores 7-8 indicate advanced frailty; and score 9 indicates that patients are terminally ill.

Assessment of frailty using the FI Lab-21 criteria

For these criteria, 20 routine blood parameters and one urine specimen finding were binary coded: 0 = normal range; 1 = deficit within normal range. Ratio of the summed number of laboratory parameters outside the normal range to the total number of parameters examined. FI -Lab21 scores were estimated at the time of admission and at the time of discharge. Data for an individual patient were recorded on a separate case sheet, which was later entered into MS -excel data sheet and subjected to statistical analysis.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences), version 21.0, a statistical analysis software. Values were presented in number (%) and mean±SD. The chi-square test was used to test the significance of the categorical data, whereas the significance of the means was tested with ANOVA. Paired t-test was used to compare the means in two different time intervals. The significance level was $p < 0.05$.

RESULTS

Of the 100 patients included, 21% were not frail, 46.0% were mildly to moderately frail, and only 33% were severely frail. FI-LAB 21 Patients' scores were assessed at admission and at discharge based on abnormalities of 21 laboratory parameters (including urinalysis).The age of patients enrolled in the study COVID -19 ranged from 65 to 90 years, and the mean age was 72.14±6.13 years. The mean age of the nonfrail patients was the lowest (66.57±1.43 years), followed by the mildly to moderately frail (70.09±2.77 years) and the severely frail (78.55±5.94 years). The age difference between patients in the above three groups with different clinical frailty was significant. When the differences

between the groups were examined, the severely frail COVID -19 patients were significantly older than the mild-to-moderately frail and nonfrail patients (Table 1).

The majority of patients were male in all frailty groups. Although the proportion of females was higher in the nonfrail group than in the mild- to- moderate frail and severely frail groups (38.1% versus 26.1% and 21.2%, respectively), this proportion was higher than that of males (Table 1).

A total of 59 patients were hypertensive, 55 had type 2 diabetes mellitus, and 32 of these patients had both hypertension and diabetes mellitus. Only 18 patients had no comorbidity. The proportion of hypertensives was significantly higher in severely frail (75.8%) and mild-to-moderately frail (56.5%) patients than in nonfrail patients (38.1%). The proportion of T2DM cases was significantly higher in severely frail (72.7%) and mild-to-moderately frail (58.7%) subjects than in nonfrail subjects (19.0%).

Cases that had both hypertension and T2DM were significantly more common in severely frail (48.5%) and mild-to-moderately frail (28.3%) than in nonfrail patients (14.3%). The majority of nonfrail cases were free of any comorbidity (57.1%) compared with the mildly to moderately frail (13.0%) and severely frail (0.0%). This difference also proved to be statistically significant. The following table shows the relationship between the FI -LAB21 score at admission (baseline) and comorbidity status at discharge, as well as the change in baseline score FI -LAB21 among cases with different comorbidities (Table 1).

Table 1: Association of Baseline characteristics and comorbidities with Frailty

		Total (N= 100)	**Mild-Moderate frail (n=46)**		**Severe frail (n=33)**		**Non-frail (n=21)**		**Statistical significance**	
			Mean	±SD	Mean	±SD	Mean	±SD	**F**	**'p'**
Age (years)	-		70.09	2.77	78.55	5.94	66.57	1.43	70.31	<0.001
			n	**%**	**n**	**%**	**n**	**%**	**χ^2**	**'p'**
Gender	Female	27	12	26.1	7	21.2	8	38.1	1.892	0.388
	Male	73	34	73.9	26	78.8	13	61.9		
Comorbidity	Hypertension	59	26	56.5	25	75.8	8	38.1	7.741	0.021
	T2DM	55	27	58.7	24	72.7	4	19.0	15.41	<0.001
	Hypertension +T2DM	32	13	28.3	16	48.5	3	14.3	7.445	0.024
	No comorbidity	18	6	13.0	0	0.0	12	57.1	29.81	<0.001

At admission FI -LAB21, scores for mild-to-moderate frailty (0.392±0.015) and severe frailty (0.392±0.164) were lower than for nonfrailty (0.419±0.174), but the difference did not prove statistically significant. At discharge FI, the LAB21 score of nonfrail patients (0.421±0.211) was higher than that of mild-to-moderate frail patients (0.371±0.130) and severe frail patients (0.398±0.155), but the difference was not statistically significant. FI -The LAB21 score (at admission and at discharge) showed no significant association with frailty (Table 2).

Table 2: Association of Frailty with FI-LAB21 scores at admission and discharge

Time	**Mild-Moderate frail (n=46)**		**Severe frail (n=33)**		**Non-frail (n=21)**		**Statistical significance (ANOVA)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**'p'**
At admission	0.392	0.015	0.392	0.164	0.419	0.174	0.305	0.738
At discharge	0.371	0.130	0.398	0.155	0.421	0.211	0.785	0.459

At admission, the FI -LAB21 score was higher in cases without comorbidity than in cases with comorbidity (0.403±0.103 vs 0.397±0.147). At discharge, the FI -LAB21 score was lower in cases without comorbidity than in cases with any comorbidity (0.362±0.164 vs 0.396±0.157). None of the differences were significant. In both groups (without comorbidity and with comorbidity), a worsening of baseline (on admission) FI -LAB21 was observed that was not statistically significant. The percentage change in baseline FI -LAB21 was higher in patients without comorbidity than in patients with comorbidity (10.19% vs. 0.09%).

At admission, the FI -LAB21 score was higher in nonhypertensives than in hypertensives (0.400±0.112 vs 0.396±0.156), but the difference proved not to be statistically significant. At discharge, hypertensives had a higher FI -LAB21 score than nonhypertensives (0.391±0.166 vs 0.389±0.146), but this difference was not statistically significant. A worsening of the FILAB21 score was observed in hypertensives and nonhypertensives, and a change in the FI-LAB21 score was not statistically significant in either group. The percentage change was higher in nonhypertensives than in hypertensives (2.80% vs. 1.33%).

The FI-LAB21 score was higher in diabetics compared with nondiabetics at both admission (0.388±0.145 vs. 0.372±0.171) and discharge (0.406±0.136 vs. 0.404±0.146), but the difference did not prove statistically significant. A statistically nonsignificant decrease in baseline FILAB21 score was observed in both diabetic and nondiabetic patients. The percent change from baseline FI -LAB21 was higher in the nondiabetic than in the diabetic cases (3.95% vs. 0.36%).

Cases with diabetes and hypertension had a higher FI -LAB21 value at both admission (0.412±0.147 vs 0.391±0.136) and discharge (0.401±0.158 vs 0.385±0.159). None of the above differences were significant. A nonsignificant worsening of the baseline FI -LAB21 score was observed in both groups, with a higher percentage worsening in patients with both comorbidities than in patients with only one/no comorbidity (2.73% vs. 1.54%). No association was observed between comorbidity status and FI -LAB21 score at admission or discharge (Table 3).

Table 3: Association of Comorbidity status on FI-LAB21 score (At admission and at Discharge)

Comorbidity Status	At admission		At Discharge		% Change (Significance)*
	Mean	SD	Mean	SD	
No comorbidity (n=18)	0.403	0.103	0.362	0.164	10.19%; p=0.148
Any comorbidity (DM/HTN) (n=82)	0.397	0.147	0.396	0.157	0.09%; p=0.981
Student 't' test	't'=0.185; p=0.853		't'=-0.827; p=0.410		
Normotensive (n=41)	0.400	0.112	0.389	0.146	2.80%; p=0.582
Hypertensive (n=59)	0.396	0.156	0.391	0.166	1.33%; p=0.771
	't'=0.131; p=0.196		't'=-0.069; p=0.945		
Non-diabetic (n=45)	0.388	0.145	0.372	0.171	3.95%; p=0.405
Diabetic (n=55)	0.406	0.136	0.404	0.146	0.36%; p=0.940
	't'=-0.634; p=0.527		't'=-1.000; p=0.320		
No comorbidity/ single comorbidity (n=68)	0.391	0.136	0.385	0.159	1.54%; p=0.697
Both DM &Htn (n=32)	0.412	0.147	0.401	0.158	2.73%; p=0.673
	't'=-0.691; p=0.491		't'=-0.456; p=0.649		

The proportion of patients who died was significantly higher in severely frail (66.7%) and mild-to-moderately frail subjects (45.7%) than in nonfrail subjects (28.6%). In addition, mortality was significantly higher in the mildly to moderately frail and the severely frail than in the nonfrail group (Table 4).

Table 4: Association of Frailty and Final Outcome (N=100)

Final Outcome	Mild-Moderate frail (n=46)		Severe frail (n=33)		Non-frail (n=21)	
	No.	%	No.	%	No.	%
Discharged	25	54.3	11	33.3	15	71.4
Expired	21	45.7	22	66.7	6	28.6
Chi-square test	χ^2=7.835; p=0.020					

Expired patients had a higher FI -LAB21 score at both admission (0.414±0.139 vs. 0.382±0.139) and discharge (0.492±0.114 vs. 0.304±0.146) compared with live patients. The difference between FI -LAB21 scores of living and deceased patients was not significant at admission. At discharge, a significant decrease in FI -LAB21 score (at admission) was observed in living patients (-20.56%). A significant increase in FI -LAB21 score (on admission) was observed in deceased patients at discharge (+15.97%) (Table 5)

Table 5: Association of Final Outcome on FI-LAB21 score (At admission and at Discharge)

Outcome	At admission		At Discharge		% Change at discharge (Paired 't' test)*
	Mean	SD	Mean	SD	
Alive	0.382	0.139	0.304	0.146	-20.56%; p<0.001
Expired	0.414	0.139	0.492	0.114	15.97%; p=0.001
Student 't' test	't'=-1.133; p=0.260		't'=-6.717; p<0.001		

For prediction of mortality, FI -LAB21 showed no significant association with mortality at admission. At discharge, FI -LAB21 score was significantly associated with prediction of outcome. A higher score of FI -LAB21 indicated a

positive outcome (mortality). The area under the curve was 0.858 (indicating a predictive accuracy of 85.8%). FI - LAB21 at discharge > 0.345 was 91.8% sensitive and 76.5% specific for predicting mortality (Table 6 and Figure 1).

Table 6: Prediction of mortality with the help of FI-LAB21 at admission and discharge

Variable	Area under curve	SE	'p'	95% CI	
				Lower bound	Upper bound
FI-LAB21 at admission	0.582	0.057	0.155	0.470	0.695
FI-LAB21 at discharge	0.858	0.041	<0.001	0.778	0.938

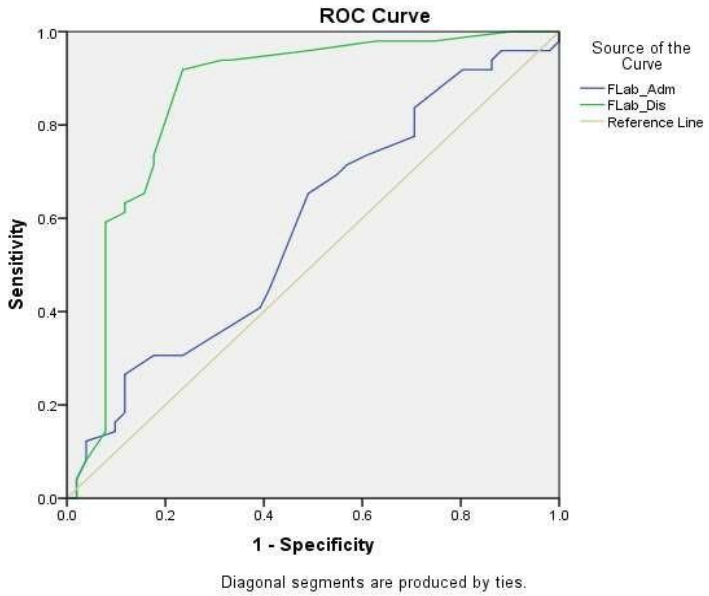

Figure 1: Receiver operating characterstic (ROC) curve plotted to assess the role of FI-LAB21 at admission and at discharge to predict mortality in the study population.

DISCUSSION

Outbreak of COVID-19 placed unprecedented demands on health care system. Health care systems across the globe collapsed, as that was not designed to deal the crisis. Apart from it, to avoid overcrowded existing health care facilities new facilities primarily to cater the needs of COVID-19 patients were established. Initial reports indicated that older adults were more susceptible to the infection, having increased severity of illness and mortality [3-6]. It was also reported that as compared to younger adults, older patients had higher requirement of ICU admissions and mechanical ventilation [21]. Decisions of management and assessment of shifting to critical care units for better recovery are generally taken on the basis of patients' physical, physiological and cognitive conditions. In view of this, NICE recommended use of clinical frailty score (CFS) in patients admitted to intensive care units. Frailty is a common syndrome with a decline in physiology, psychology and cognition [22]. An increase in risk of falls, disability, frequency of hospitalization and mortality is commonly observed in frail individuals [23]. Risk of frailty is higher among elderly, but it can develop at any age. The concept of assessment of Frailty for decision making in ICUs using Clinical Frailty Scale has been well established [24, 25]. After recommendation of NICE assessment frailty for decision making on COVID-19 patients for treatment to reduce the morbidity and mortality, frailty instead of old age had been adopted for treatment. Predictive role of frailty for mortality had been studied in different populations using different study designs. We could not trace even a single study showing association of frailty with COVID-19 outcomes therefore, the present study was proposed to find association of frailty and outcomes of COVID-19 in Indian scenario. Clinical Frailty Score (CFS) a well-recognised, reliable and validated tool to assess frailty had been used to assess the frailty. An attempt has been made to verify the utility of FILab-21 which identifies physiological status of patients for frailty can be opted in COVID-19 like pandemic. We could not trace use of FILab-21 for assessment of frailty in COVID-19 patients in the literature.

All patients included in the study were assessed for frailty using a 9-point clinical frailty scale. Only 21% were not frail (CFS 1-3), none were at risk (CFS 4), 46% had mildto moderate frailty (CFS 5-6), and 33% were severely frail (CFS 7-8). Therefore, the incidence of frailty in COVID -19 patients in the present study was 79% and that of severe frailty was 33%. A review of other studies shows that the incidence of frailty ranges from 7% to 85.9% [26, 27].

Compared with the present study (79% frail; 33% severely frail: CFS 7-8), variation in the incidence of frailty was reported, depending strongly on patient characteristics and method of observation. In addition, there are differences in the

method used to assess frailty. Similar to the present study, the incidence of frailty was 70.8% [28], 79% [29], 72% [30], and 28.8% [31], and 35.8% severely frail [32].

All of these studies were observational studies of COVID -19 cases, with the exception of the study by Mueller et al,81 which was performed in COVID -19 COVID -19 surviving patients. A study reported that the 85.9% frailty, included patients aged ≥80 years, with a female predominance [27]. The higher incidence reported by the GMRC (83.8%)75 was based on records from 55 hospitals in 12 countries and showed a lower predominance of men compared with the present study (55.1% vs 73%). Another study found that the frailty in 54% of cases, with assessment of frailty based on a record-based multidimensional prognostic index [33]. In their study, the majority of patients were female, and the mean age of patients was 81 years. A lower incidence was also found in several multicenter studies and meta-analyses 23.4% [34], 7% [26], 19.4% [35], and 51.4% [36]. Thus, the results of the present study are consistent with most of the current literature, considering the differences in patient profile and study design. In the present study, we evaluated FILab-21 scores at the time of admission and at discharge/mortality. In the absence of similar data in the available literature, no comments could be made.

In the present study, we found that severely frail patients were significantly older than their non-frail and mild to moderately frail counterparts (78.55±5.94 vs. 66.57±1.43 & 70.09±2.77 years). Various previous studies had also confirmed the results of the present study [29, 31, 33 & 35].

In the present study, we found no significant association between sex and frailty. Overall, a higher proportion of frailty and severe frailty was observed in men than in women (82.2% vs 70.4% and 35.6% vs 25.9%, respectively), but the difference in the degree of frailty between men and women was not significant. None of the other investigators had found a significant association between frailty and male sex. A study reported that the association between female sex and frailty [37].

In the present study, FILab-21 scores were determined at admission and at discharge. FILab-21 scores of nonfrail, mild-to-moderate frail, and severely frail patients were comparable at both admission and discharge. Because comparative data were not available in the other studies, we could not comment on this issue. However, the usefulness of FILab-21 in COVID -19 patients for frailty is doubtful.

In the present study, we observed that more comorbidities such as hypertension, type 2 DM, and both hypertension and T2DM were present compared with nonfrail, mild-to-moderately frail, and severely frail patients. In the elderly, an overlap of comorbidity and frailty is often observed, which is reflected in functional status. Frailty is defined as impairment of multiple, interrelated organ systems leading to decreased homeostatic reserve and increased vulnerability to stress [10]. The role of comorbidities in clinical frailty and mortality has been discussed by several investigators who reported diabetes [38], hypertension [35], low eGFR [31, 38], CVD [31, 35, 37 & 38] as risk factors for frailty and mortality. The collective role of comorbidities has been assessed by different authors using the Charlson comorbidity index [19, 39]. In the present study, we compared FILab-21 scores in different comorbidities, which showed no significant association.

Of 100 patients enrolled in the present study, 49 (49%) died. The mortality rate was significantly higher in severely frail and mild-to-moderately frail patients than in nonfrail patients (66.7%, 45.7% vs. 28.6%, respectively). This difference was statistically significant. The mortality rate in frail patients was 54.4%. From other studies, the risk of mortality is higher in frail COVID -19 patients than in nonfrail patients, according to the current literature.

At admission and at discharge, FILab-21 scores of patients with expired disease were higher than those of patients with normal disease, but this difference was not significant at admission, whereas at discharge, a significant difference was found between FILab-21 scores of patients with expired and discharged disease. Higher FILab-21 values are indicative of higher abnormal parameters in discharged patients.

At discharge/mortality, a negative change in FILab-21 score was observed in living patients, whereas an increase in FILab-21 score was observed in deceased patients, suggesting that an increase in abnormal parameters may be indicative of mortality. The ROC analysis of FILab-21 score to predict mortality showed that FILab-21 score at admission showed no significant association with mortality, whereas FILab-21 score at discharge >was 0.345 to 91.8% sensitive and 76.5% specific for predicting mortality.

Limitation of the study

The lack of literature on FILab-21 scores to predict outcomes during COVID -19 was a barrier to comparing the results of the present study with the current literature.

Scope of the study

There is an increasing need to describe a patient's clinical condition in terms of functional capacity, such as frailty. Frailty is an age-related syndrome that decreases physiological and cognitive reserve. As a result, frailty increases people's vulnerability to injuries such as infection and trauma.

CONCLUSION

Among the frail patients, the severely frail cases (based on CFS) were significantly older than the mild-to-moderate and the nonfrail COVID -19 cases. Patient gender did not show a significant association with frailty. FILab-21 scores (at admission and discharge) showed no significant association with CFS frailty. Among concomitant diseases, hypertension, T2DM, and hypertension and T2DM were significantly associated with frailty. The mortality rate was significantly higher in severely frail (66.7%) and mild-to-moderately frail (45.7%) patients than in nonfrail (28.6%) patients. FILab-21 score at admission showed no significant association with mortality, but at discharge, expired cases had significantly higher FILab-21 scores. The FILab-21 score at discharge to predict mortality was recorded. The FILab-21 score > 0.345 proved to be 91.8% sensitive and 76.5% specific for predicting mortality.

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