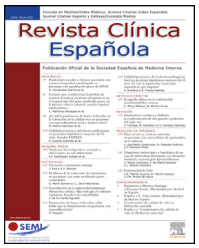
Revista Clínica Española xxx (xxxx) xxx–xxx

Revista Clínica Española

www.elsevier.es/rce



ORIGINAL ARTICLE

The impact of frailty on intra-hospital survival in older patients with COVID-19 infection: the importance of early identification. SEMI-COVID National Registry

A. López-Sampalo[a], H. Hernández-Negrín[a], M.-R. Bernal-López[a,b,*], M. Rubio-Rivas[c], M.D. Martín-Escalante[d], P. Wikman-Jogersen[e], A. García-Reyne[f], R.F.-M. Martinez[g], M. Gómez-Antúnez[h], J. Luis Beato-Pérez[i], J. David Torres-Peña[j], J. Ángel Martín-Oterino[k], J. Loureiro-Amigo[l], J. Vicente de la Sota[m], R. Gil-Sánchez[n], M.L.-L. Reboiro[o], B. Bernal-Román[p], J. Fernández-Sola[q], F. Amorós-Martínez[r], N. Vicente-López[s], R. Valle-Bernard[t], A. López-Ruiz[u], J.-M. Ramos-Rincón[v,1], R. Gómez-Huelgas[a,b,1]

[a] *Internal Medicine Department, Regional University Hospital of Málaga, Instituto de Investigación Biomedica de Málaga (IBIMA-Plataforma BIONAND), University of Málaga (UMA), Málaga, Spain*
[b] *Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain*
[c] *Internal Medicine Department, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, University of Barcelona, Barcelona, Spain*
[d] *Internal Medicine Department, Costa del Sol Hospital, Marbella, Málaga, Spain*
[e] *Internal Medicine Department, San Juan University Hospital, Alicante, Spain*
[f] *Internal Medicine Department, 12 de Octubre University Hospital, Madrid, Spain*
[g] *Internal Medicine Department, Cabueñes University Hospital, Gijón, Spain*
[h] *Internal Medicine Department, Gregorio Marañón University Hospital, Madrid, Spain*
[i] *Internal Medicine Department, Albacete University Hospital Complex, Albacete, Spain*
[j] *Internal Medicine Department, Reina Sofia University Hospital, Córdoba, Spain*
[k] *Internal Medicine Department, Salamanca University Health Care Complex, Salamanca, Spain*
[l] *Internal Medicine Department, Moisès Broggi Hospital, Sant Joan Despí, Barcelona, Spain*
[m] *Internal Medicine Department, Infanta Cristina University Hospital, Parla, Madrid, Spain*
[n] *Internal Medicine Department, La Fe University Hospital, Valencia, Spain*
[o] *Internal Medicine Department, Regional Hospital of Monforte de Lemos, Monforte de Lemos, Lugo, Spain*
[p] *Pneumology Department, Doctor José Molina Orosa University Hospital, Arrecife, Lanzarote, Spain*
[q] *Internal Medicine Department, Clinic Hospital, Barcelona, Spain*
[r] *Internal Medicine Department, Vinalopó Hospital, Alicante, Spain*
[s] *Internal Medicine Department, Sureste University Hospital, Arganda del Rey, Madrid, Spain*
[t] *Internal Medicine Department, Sierrallana Hospital, Torrelavega, Cantabria, Spain*

* Corresponding author.
E-mail address: rosa.bernal@ibima.eu (M.-R. Bernal-López).
[1] Dr. Ricardo Gómez-Huelgas and Dr. José-Manuel Ramos-Rincón have contributed equally to this work and share the last authorship.

https://doi.org/10.1016/j.rceng.2023.07.004

Please cite this article as: A. López-Sampalo, H. Hernández-Negrín, M.-R. Bernal-López et al., The impact of frailty on intra-hospital survival in older patients with COVID-19 infection: the importance of early identification. SEMI-COVID National Registry, Revista Clínica Española, https://doi.org/10.1016/j.rceng.2023.07.004

[u] *Internal Medicine Department, Axarquía Hospital, Vélez-Málaga, Málaga, Spain*
[v] *Department of Clinical Medicine, Miguel Hernandez University of Elche, Alicante, Spain*

Received 21 May 2023; accepted 24 May 2023

KEYWORDS
Frailty;
Prognosis;
Survival;
COVID-19;
Older people

Abstract:
Background: Emerging evidence suggests that frailty may be a significant predictor of poor outcomes in older individuals hospitalized due to COVID-19. This study aims to determine the prognostic value of frailty on intrahospital patient survival.
Methods: This observational, multicenter, nationwide study included patients aged 70 years and older who were hospitalized due to COVID-19 in Spain between March 1 and December 31, 2020. Patient data were obtained from the SEMI-COVID-19 Registry of the Spanish Society of Internal Medicine. Frailty was assessed using the Clinical Frailty Scale. The primary outcome was hospital survival. Cox proportional hazards models were used to assess predictors of survival.
Results: A total of 1,878 participants (52% men and 48% women) were included, with 1,351 (71.9%) survivors and 527 (28.1%) non-survivors. The non-survivor group had higher mean age (83.5 vs. 81 years), comorbidities (6.3 vs. 5.3 points on the Charlson index), degree of dependency (26.8% vs. 12.4% severely dependent patients), and frailty (34.5% vs. 14.7% severely frail patients) compared to survivors. However, there were no differences in terms of sex. Our results demonstrate that a moderate-severe degree of frailty is the primary factor independently associated with shorter survival [HR 2.344 (1.437—3.823; $p < 0.001$) for CFS 5—6 and 3.694 (2.155—6.330; $p < 0.001$) for CFS 7—9].
Conclusion: Frailty is the main predictor of adverse outcomes in older patients with COVID-19. The utilization of tools such as the Clinical Frailty Scale is crucial for early detection in this population.

PALABRAS CLAVE
Fragilidad;
Pronóstico;
Supervivencia;
COVID-19;
Pacientes mayores

Impacto de la fragilidad en la supervivencia intrahospitalaria en pacientes mayores con infección por COVID-19: la importancia de su identificación temprana. Registro Nacional SEMI-COVID

Resumen
Introducción: La evidencia reciente sugiere que la fragilidad puede ser un importante predictor de resultados adversos en personas mayores hospitalizadas por COVID-19. El objetivo de este estudio es determinar el valor pronóstico de la fragilidad en la supervivencia intrahospitalaria de estos pacientes.
Métodos: Estudio observacional, multicéntrico y de ámbito nacional de pacientes ≥70 años hospitalizados a consecuencia de la COVID-19 en España desde el 1 de marzo hasta el 31 de diciembre de 2020. Los datos de los pacientes se obtuvieron del Registro SEMI-COVID-19 de la Sociedad Española de Medicina Interna. Se utilizó la Escala de Fragilidad Clínica para evaluar la fragilidad. El resultado primario fue la supervivencia hospitalaria. Se realizó un modelo de riesgos proporcionales de Cox para evaluar los predictores de supervivencia.
Resultados: Se incluyeron 1.878 participantes (52% hombres y 48% mujeres). 1.351 (71,9%) supervivientes y 527 (28,1%) no supervivientes. El grupo de no supervivientes presentaba en comparación con los supervivientes una media de edad superior (83,5 frente a 81 años), más comorbilidades (6,3 frente a 5,3 puntos en el índice de Charlson), mayor grado de dependencia (26,8% frente a 12,4% de pacientes con dependencia severa) y de fragilidad (34,5% frente a 14,7% de pacientes con fragilidad severa), sin embargo, no hubo diferencias en cuanto al sexo. Nuestros resultados muestran que un grado de fragilidad moderado-grave es el principal factor asociado de forma independiente con una menor supervivencia [HR 2,344 (1,437—3,823; $p < 0,001$) para SFC 5—6 y 3,694 (2155—6,330; $p < 0,001$) para SFC 7—9.].

Conclusiones: La fragilidad es el principal predictor de resultados adversos en pacientes mayores con COVID-19. El uso de herramientas como la CFS es fundamental para la detección precoz de fragilidad en esta población.

Introduction

The COVID-19 pandemic has had an immense impact on the elderly, who are among the most vulnerable and affected groups. This population experiences a higher proportion of severe cases and complications during infection [1] and exhibits intrinsic and extrinsic factors that contribute to increased clinical fragility and susceptibility to infectious processes, such as weakened immune systems or immunosenescence,[2] heightened comorbidity,[3] malnutrition,[4] and a higher rate of institutionalization.

Since the onset of the COVID-19 pandemic, advanced age has been identified as one of the strongest risk factors for poor outcomes, complications, and mortality.[5–7] Age is an easily measurable prognostic marker; however, its prognostic utility by itself is limited.[8] In this regard, emerging evidence suggests that frailty may be a significant predictor of poor outcomes in older people hospitalized due to COVID-19.[9,10] Frailty has also been used for clinical decision-making during this pandemic,[11] but further clinical research is still needed to determine the usefulness of frailty screening in predicting adverse disease.

Frailty is defined as ä medical syndrome with multiple causes and contributors characterized by diminished strength, endurance, and reduced physiological function, which increases an individual's vulnerability to developing increased dependency and/or death.[12] The likelihood of frailty increases with age, estimated to affect around 40% of older patients.[13] Fried's frailty criteria are widely used for diagnosing frailty.[14] According to these criteria, a diagnosis of frailty is established if the patient meets three of the following criteria: unintentional weight loss, exhaustion, muscle weakness, motor slowness, and low activity. Over the years, multiple instruments have been developed to assess frailty, including rapid detection scales that are more feasible in clinical practice and require only a few minutes of application, such as the Clinical Frailty Scale (CFS)[15] and the FRAIL scale.[16]

The relationship between the degree of pre-infection clinical frailty and the progression of COVID-19 has been the subject of several studies to date. However, most studies assessing the prognostic capacity of clinical frailty have either been conducted in the general population or, if they do evaluate prognostic factors in older patients, have not included the degree of frailty. These studies have examined the relationship between frailty and mortality, hospital infection rates, intensive care admission rates, and disease phenotypes.[10,17,18]

Other factors, such as advanced age, male sex, severe functional dependence, and comorbidities like hypertension, diabetes mellitus, and obesity, as well as analytical parameters (C-reactive protein, lymphopenia, neutrophilia, etc.), clinical parameters at admission (hypoxia, high SOFA score, temperature, etc.), and the presence of radiological abnormalities, have also been identified as the main risk factors for poor outcomes in older people with COVID-19 infection.[19–21]

Systematic frailty assessment in older patients with COVID-19 infection allows for the early identification of frail elderly patients. This enables better care for those at higher risk of severe disease and facilitates improved resource allocation. Therefore, the objectives of this study in older patients hospitalized due to COVID-19 infection are as follows: a) to determine the prognostic value of frailty on intrahospital patient survival compared to other previously identified predictors of poor prognosis, and b) to emphasize the importance of early detection of frailty in this population.

Materials and methods

Study design and recruited population

This was an observational, multicenter, nationwide study of patients aged ≥70 years old who were hospitalized due to COVID-19 in Spain from March 1 to December 31, 2020. Patient data was obtained from the Spanish Society of Internal Medicine's SEMI-COVID-19 Registry, which includes 150 Spanish hospitals. The registry encompasses all consecutive patients aged ≥18 years old admitted to hospitals with confirmed COVID-19 through microbiological testing using reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab samples, sputum specimens, or bronchoalveolar lavage. For this study, we focused on the subpopulation of patients aged ≥70 years old.

Definition of variables

The SEMI-COVID-19 Registry retrospectively collects data from the initial admission of patients aged ≥18 years with confirmed COVID-19. The data include sociodemographic information, previous medical history, routine treatments, clinical presentation, clinical condition, laboratory test results, radiological findings, clinical management, in-hospital complications, length of hospital stay, early readmissions, referral to long-term care or skilled nursing facilities, and in-hospital deaths. More detailed information about the justification, objectives, methodology, and preliminary results of the SEMI-COVID-19 Registry has been published in this journal (Vol. 220. No. 8.).[22] Clinicians collected the data retrospectively using an online electronic data capture system.

To assess preadmission functional status, we used the Barthel Index. A score of 100—91 indicates independence or slight dependency, 90—61 indicates moderate dependence, and ≤60 indicates severe dependency.[23] The comorbidity burden was assessed using the age-adjusted Charlson Comorbidity Index (CCI).[24] The diagnosis of dementia was based on DSM-5 criteria.[25] Atherosclerotic cardiovascular disease encompassed a history of ischemic cardiopathy (myocardial infarction, acute coronary syndrome, angina, or coronary revascularization), cerebrovascular disease (stroke, transient ischemic attack), or peripheral arterial disease (intermittent claudication, revascularization, lower limb amputation, or abdominal aortic aneurysm). Nonatherosclerotic cardiovascular disease included atrial fibrillation and heart failure. Obesity was defined as a body mass index ≥30 kg/m^2. Hypertension, diabetes mellitus, and dyslipidemia were considered present if there was a prior clinical diagnosis or if the patients had been receiving pharmacological treatment for these conditions. Chronic pulmonary disease was defined as a diagnosis of chronic obstructive pulmonary disease and/or asthma. Malignancy included solid tumors and/or hematologic neoplasia (excluding nonmelanoma skin cancer). Moderate-to-severe renal disease was defined as an estimated glomerular filtration rate <45 mL/min/1.73 m^2 according to the CKD-EPI equation.[26]

Preadmission comorbidity data were collected from each patient's electronic medical record at each hospital. Laboratory data (blood gases, metabolic panel, complete blood count, coagulation) and diagnostic imaging tests were collected at admission.

The variables for analysis were selected based on recent studies on COVID-19 that identified them as indicators of poor prognosis.[19–21] These variables included age, male sex, level of severe dependence (Barthel <60), clinical diagnosis of coronary heart disease, diabetes, and hypertension; smoking (previous or current), oxygen saturation <90%, temperature ≥37.8 °C at admission, and blood biomarkers (lactate dehydrogenase (LDH) ≥500 U/L, C-reactive protein (CRP) ≥80 mg/L, neutrophil count ≥7.5 × 103/μL, and lymphocyte count <0.800 × 103/μL) as well as bilateral pulmonary infiltrates on chest X-ray.

Frailty was assessed using the Clinical Frailty Scale (CFS).[15] The assessment was based on the patient's condition two weeks before hospital admission. The CFS is an ordinal hierarchical scale that ranks frailty from 1 to 9, with a score of 1 indicating very fit, 2 indicating well, 3 indicating managing well, 4 indicating vulnerable, 5 indicating mildly frail, 6 indicating moderately frail, 7 indicating severely frail, 8 indicating very severely frail, and 9 indicating terminally ill. Due to the inadequate number of events for each score, the scores were grouped as follows for analysis: 1–2 (fit), 3–4 (becoming vulnerable, but not frail), 5–6 (initial signs of frailty but with some degree of independence), and 7–9 (severe or very severe frailty). These groupings were selected to align with the clinical descriptions outlined in the CFS and were considered reasonable severity groupings for frailty.

The primary outcome of the study was intrahospital survival, defined as the time from hospital admission due to COVID-19 to in-hospital mortality. For patients diagnosed with COVID-19 while already being hospitalized (hospital-acquired or nosocomial infection), the date of diagnosis was used instead of the date of admission.

Statistical analysis

Qualitative variables were presented as absolute and relative frequencies and compared using the chi-square test or Fisher's exact test, as appropriate. Quantitative variables were expressed as mean and standard deviation and compared using Student's t-test for independent groups.

To assess the prognostic value of frailty on patient survival, a multivariate Cox proportional hazards analysis was conducted. This analysis included variables that showed a significant association in the univariate analysis, as well as other variables of recognized prognostic value and potentially confounding factors reported in the literature, particularly those found in a previous article based on this COVID-19 patient registry.[19] Kaplan–Meier curves were generated to visually represent patient survival according to frailty categories. A significance level of 0.05 (95% confidence level) was assumed. The data were stored and analyzed using the SPSS statistical package, version 25, for Windows.

Ethical aspects

Informed consent was obtained from all patients. In cases where biosafety concerns or patient discharge had occurred, verbal informed consent was requested and documented in the medical records. Data confidentiality and patient anonymity were strictly maintained in accordance with Spanish regulations governing observational studies. Patient identifiable information was removed before analyzing the database, ensuring that individual patients cannot be identified either in this article or in the database.

Results

In the SEMI-COVID-19 Registry, a total of 1,920 patients aged ≥70 years who had been hospitalized due to COVID-19 infection between March 1 and December 31, 2020 were identified, and their degree of frailty was assessed. Forty-two participants were excluded due to incomplete registration of minimum clinical characteristics. Ultimately, the study included 1,878 participants of both sexes, with 52% men and 48% women. Among the included patients, 1,351 (71.9%) were discharged alive from the hospital, while 527 (28.1%) died during their hospital stay. There were no significant differences in the survival rates between males and females (Table 1).

The clinical and demographic characteristics of the population are shown in Table 1. The mean age of the population was 81.7 ± 6.9 years, being higher in the group of non-survivors (83.5 vs. 81 years, p < 0.001). The most prevalent comorbidities were hypertension (75.2%), dyslipidaemia (51.9%), diabetes (32%), atrial fibrillation (21%), and dementia (20.8%). The proportion of comorbidities such as dyslipidaemia, diabetes mellitus with target organ involvement, atrial fibrillation, dementia, degenerative neurological disease, and heart failure was significantly higher in the non-survivor group (p < 0.001). However,

Table 1 Clinical and demographical characteristics in patients ≥70 years hospitalised due to COVID-19.

Variables	All patients (n = 1878)	Dead (n = 527)	Alive (n = 1351)	*p*
Age, years (mean ± standard deviation)	81.7 ± 6.9	83.5 ± 7.0	81.0 ± 6.8	<0.001
Sex (%)				0.012
Female	901 (48.0)	228 (43.3)	673 (49.8)	
Male	977 (52.0)	299 (56.7)	678 (50.2)	
BMI (mean ± standard deviation)	28,8 ± 4.9	29.0 ± 5.4	28.7 ± 4.7	0.570
Smoking status (%)	581 (31.3)	185 (35.7)	396 (29.6)	0.010
Comorbidities (%)				
Arterial hypertension	1412 (75.2)	412 (78.2)	1000 (74)	0.061
Dyslipidaemia	974 (51.9)	299 (56.7)	288 (43.3)	0.008
Diabetes without target organ damage	415 (22.1)	108 (20.5)	307 (22.7)	0.295
Diabetes with target organ damage	187 (10.0)	75 (14.2)	112 (8.3)	<0.001
Atrial fibrillation	395 (21.0)	145 (27.5)	250 (18.5)	<0.001
Dementia	390 (20.8)	165 (31,3)	225 (16.7)	<0.001
Degenerative neurological disease	322 (17.2)	127 (24.2)	195 (14.4)	<0.001
Heart failure	221 (11.8)	100 (19.0)	121 (9.0)	<0.001
COPD	195 (10.4)	65 (12.4)	130 (9.6)	0.082
Moderate-severe Chronic renal failure	184 (9.8)	86 (16.3)	98 (7.3)	<0.001
Acute myocardial infarction	173 (9.2)	78 (14.8)	95 (7.0)	<0.001
Peripheral vascular disease	114 (6.1)	41 (7.8)	73 (5.4)	0.054
Asma	113 (6.0)	29 (5.5)	84 (6.2)	0.558
Obstructive sleep apnea syndrome	104 (5.6)	32 (6.1)	72 (5.4)	0.529
Cerebrovascular disease	90 (4.8)	40 (7.6)	50 (3.7)	<0.001
Neoplasia with metastasis	38 (2.0)	16 (3.0)	22 (1.6)	0.052
Charlson Index (mean ± standard deviation)	5.6 ± 2.0	6.3 ± 2.2	5.2 ± 1.9	<0.001
Level of dependency (%)				<0.001
Mild	1171 (62.5)	231 (43.9)	940 (69.7)	
Moderate	395 (21.1)	154 (21.1)	241 (17.9)	
Severe	114 (16.4)	141 (26.8)	167 (12.4)	
CFS (%)				<0.001
1–2: very fit/fit	174 (9.3)	20 (3.8)	154 (11.4)	
3–4: managing well/vulnerable	795 (42.3)	145 (27.5)	650 (48.1)	
5–6: mildly frail/moderately frail	529 (28.2)	180 (34.2)	349 (25.8)	
7–9: severely frail/very severely frail/terminally ill	380 (20.2)	182 (34.5)	198 (14.7)	

BMI, body mass Index; COPD, chronic obstructive pulmonary disease; CFS, clinical frailty scale.
Variables are expressed as mean ± standard deviation (SD) and the *p* value.

although the proportion of cases with hypertension and COPD was also higher in the non-survivor group, no significant differences were found compared to survivors. Charlson index was high in all population, but more in the non-survivor group (6.3 vs. 5.3 points, p < 0.001). Most patients (62,5%) were independent or with a middle level of dependence; nonetheless, the proportion of patients with a moderate or severe level of dependence was higher among non-survivors (34.2% vs 25.8% patients with moderate frailty, and 34.5% vs. 14.7% patients with severe frailty, respectively, p < 0.001).

Regarding the degree of frailty, 174 patients (9.3%) were classified as very fit/fit (CFS 1–2); 795 patients (42.3%) as vulnerable (CFS 3–4); 529 patients (28.9%) were classified as moderately fragile (CFS 5–6) and 380 patients (20.2%) as severely fragile or terminal (CFS 7–9). The proportion of patients with moderate or severe frailty is significantly higher in non-survivors (p < 0.001)

A higher proportion of patients in the non-survivor group had significantly higher levels of leukocytes, neutrophils, CRP, creatin, LDH, ferritin, and procalcitonin (Table 2) than survivors (p < 0.001). Non-survivors also had higher lymphopenia and higher D-Dimer values, although this did not reach significance. Hypoxemia (Oxygen saturation <90%) was more frequent in non-survivor group (p < 0.001). Radiological findings (condensations, bilateral infiltrates and pleural effusion) were significantly more frequent in the non-survivor group (p < 0.001).

Frailty was associated with higher all-cause mortality after adjustment for age, sex, and comorbidities, showing worsening of clinical outcome with increased frailty (Table 3 and Fig. 1). The crude HR for time from hospital admission to mortality was 1.634 (95% CI 1.023–2.611; p 0.04) for CFS 3–4; 2,887 (1,816–4,591; p < 0.001) for CFS 5–6 and 5,557 (3,493–8,841; p < 0.001) for CFS 7–9, all compared to CFS 1–2. The adjusted HR was 1.458 (95% CI 0.903–2.355; p 0.001) for CFS 3–4; 2,344 (1,437–3,823; p < 0.001) for CFS 5–6 and 3,694 (2,155–6,330; p < 0.001) for CFS 7–9. Elevated CRP, lymphopenia, neutrophilia, hypoxemia, and bilateral chest X-ray infiltrates were also significantly associated with mortality (p < 0.001). Severe dependence was also significantly associated with mortality in the univariate analysis with a crude HR of 2.409 (1.984–2.926; p < 0.001);

Table 2 Laboratory, physical examination, and radiological findings in patients ≥70 years hospitalised because of COVID-19.

Variables	All patients (n = 1878)	Dead (n = 527)	Alive (n = 1351)	*p*
Temperature, ^{0}C (mean ± standard deviation)	36.7 ± 0.8	36.7 ± 0.83	36,6 ± 0.88	0.092
Oxygen saturation <90% (mean ± standard deviation)	92.9 ± 5.4	91.4 ± 6.8	93.5 ± 4.7	<0.001
Ches x-ray findings (%)				
Pneumonic condensation				<0.001
Unilateral	172 (10.6)	51 (12.2)	121 (10.1)	
Bilateral	312 (19.3)	134 (32.1)	178 (14.8)	
Interstitial lung infiltrates				<0.001
Unilateral	126 (7.8)	23 (5.5)	103 (8.6)	
Bilateral	969 (59.9)	299 (71.7)	670 (55.8)	
Pleural effusion				<0.001
Unilateral	56 (3.5)	27 (6.5)	29 (2.4)	
Bilateral	32 (2.0)	16 (3.8)	16 (1.3)	
Analytics (mean ± standard deviation)				
Haemoglobin, g/dL	12.7 ± 2.0	12.4 ± 2.2	12.8 ± 2.0	<0.001
Leukocytes, $10^3/\mu$L	7665.3 ± 4929.8	8871 ± 6708	7196 ± 3938	<0.001
Neutrophils, $10^3/\mu$L	5901.8 ± 4333.5	7038 ± 3888.4	5460 ± 5144.0	<0.001
Lymphocytes, $10^3/\mu$L	1169.9 ± 2657.6	1094.3 ± 2729.9	1099.1 ± 2629.5	0.444
Platelets, $10^3/\mu$L	200 ± 90	197 ± 91	202 ± 89	0.244
C-reactive protein, mg/L	90.1 ± 85.6	115.7 ± 101.2	80.9 ± 76.6	<0.001
Creatinine, mg/dL	1.3 ± 1.0	1.6 ± 1.2	1.2 ± 0.9	<0.001
LDH, U/L	357.5 ± 230.2	407.4 ± 302.7	338.7 ± 193.0	<0.001
Ferritin, μg/L	748.2 ± 890.5	996.7 ± 1197.8	663.5 ± 739.8	<0.001
Albumin, g/dL	3.4 ± 3.5	3.2 ± 0.5	3.5±-0.5	<0.001
Procalcitonin, ng/mL	0.54 ± 2.77	0.93 ± 3.6	0.39 ± 2.3	0.014
D-dimer, ng/mL	2376.9 ± 14956.5	3749.9 ± 27261.2	1869.4 ± 5584.4	0.145

LDH, lactate deshydrogenase.
Variables are expressed as mean ± standard deviation (SD) and *p* value.

Table 3 Prognostic factors for in-hospital survival. Univariate and multivariate analysis.

Variables	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	*p*
CFS 1–2	Reference					
CFS 3–4	1.634	1.023–2.611	0.040	1.458	0.903–2.355	0.123
CFS 5–6	2.887	1.816–4.591	<0.001	2.344	1.437–3.823	<0.001
CFS 7–9	5.557	3.493–8.841	<0.001	3.694	2.155–6.330	<0.001
C-reactive protein ≥ 80 mg/l	2.196	1.844–2.613	<0.001	1.835	1.530–2.201	<0.001
Lymphocytes < $0.800 \times 10^3/\mu$L	1.829	1.537–2.175	<0.001	1.706	1.418–2.051	<0.001
Neutrophils ≥ $7.5 \times 10^3/\mu$L	1.676	1.412.990	<0.001	1.503	1.256–1.799	<0.001
$SatO_2$ <90%	1.665	1.371–2.020	<0.001	1.492	1.218–1.827	<0.001
Bilateral interstitial lung infiltrates on x-ray	1.559	1.255–1.936	<0.001	1.375	1.092–1.732	0.007
Severe dependency	2.409	1.984–2.926	<0.001	1.184	0.879–1.595	0.266
Charlson index	1.154	1.115–1.194	<0.001	1.067	1.023–1.113	0.003
Age, years	1.057	1.044–1.070	<0.001	1.032	1.018–1.047	0.000
Female Sex	1.119	0.857–1.212	0.828	0.989	0.821–1.191	0.906

however, in the multivariate analysis this association was not significant adjusted HR 1.184 (0.879–1.595; p 0.266).

Discussion

Our study determines the importance of early detection of frailty in older patients hospitalised due to COVID-19, considering it as main risk factor associated with adverse outcomes compared to other risk factors already identified in previous studies. The main predictors of poor prognosis during the acute phase of infection have been described in previous studies. However, most of them have been performed in the general population and only some have targeted the older patient population or have evaluated the degree of frailty.[17]

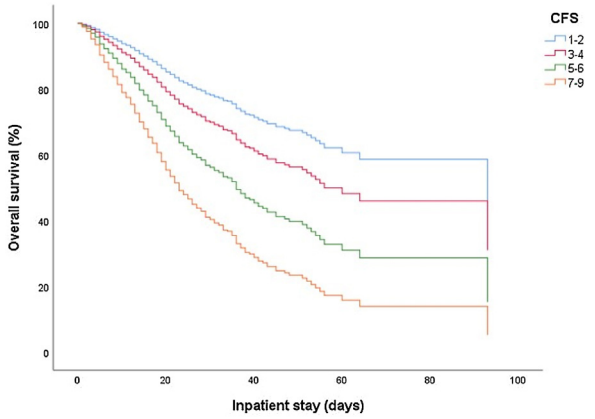


Figure 1 Overall survival by CFS category.

Older age is associated with increased mortality but is not sufficient on its own for risk stratification in patients with COVID-19 and is subject to ethical controversy.[11] Pre-admission functional status plays an important role in the evolution of this patient profile, especially those with a moderate-severe degree of frailty who are at higher risk of adverse outcomes. This relationship between frailty and increased mortality has been extensively studied in other diseases. In COVID-19 an increasing number of studies have identified frailty as one of the main prognostic factors of the disease, but more evidence is still needed.

Previously, the SEMI-COVID registry[19] had identified the main predictors of poor prognosis in very older patients (>80 years) hospitalised due to COVID-19 infection and this study was the first one to identify the prognostic significance of pre-admission clinical status on the outcome of geriatric patients, finding that a severe degree of dependency (defined as a Barthel Index $\leq$60) was an independent predictor of mortality. Nonetheless, one of the main limitations of this study was that it did not evaluate frailty. Advanced age, severe level of dependency, male sex, certain laboratory, and chest X-ray abnormalities were identified as the main predictors of poor clinical outcome in this population. In contrast, comorbidities were not associated with increased mortality. Our data reflect concordance with the results of this study except for some aspects. No association was found between intrahospital survival and sex or level of severe dependency. However, a high degree of comorbidity (defined by Charlson index $\geq$4) was associated with lower intrahospital survival.

Studies assessing frailty in COVID-19 such as the COPE study,[17] and others[27] demonstrated that frailty was associated with mortality and longer hospital stay, showing a worsening of clinical outcome with increasing frailty. Our results do not only confirm these assertions, but also establish the presence of moderate-severe frailty as the main prognostic factor independently associated with all-cause hospital survival compared to the other factors identified in previous studies. In addition, there is a direct relationship between a higher degree of frailty and lower intrahospital survival.

The assessment of the degree of frailty was carried out using the quantitative method CFS, which is the most widely used in other studies.[28,29] The CFS is a reliable and potentially useful screening tool to identify frailty. It is also easily applicable even in a situation of limited human resources and increasing demand for medical services,[30] as it was the case in the COVID-19 pandemic. Other frailty measures are available for the assessment of frailty in hospitalised patients but are either more time consuming to apply or rely on routinely collected data to score frailty.[31] The National Institute for Health and Care Excellence (NICE) published in 2020 the COVID-19 rapid guidelines for adult critical care, recommending the use of the CFS in patients aged 65 and over to aid clinical decision making and avoid age discrimination.[32]

Therefore, the early assessment of frailty represents a valuable opportunity to provide higher quality care to older adults with COVID-19. Early detection and careful monitoring of frailty can alert us to the possibility of adverse outcomes and help us to provide appropriate clinical management in this patient profile. The initial approach to these patients should incorporate an appropriate functional assessment including the evaluation of the degree of frailty. In addition, we would like to emphasise the importance of the use of the CFS scale as a predictor of unfavourable events in this population.

This study has some limitations. First, this is a retrospective series focusing on hospitalised patients. Since these patients had more severe disease and a higher mortality rate, our data may overestimate the overall mortality in the totality of adults over 70 years of age with COVID-19. Second, as a retrospective cohort study, the data were collected by a large number of investigators, which could have led to heterogeneity in data entry and validation.

Conclusion

In older patients hospitalised due to COVID-19 infection, the degree of frailty is the main predictor of intrahospital survival, showing that it increases the risk of all-cause mortality after adjustment for age, comorbidities, and other prognostic factors related to the severity of the infection. These findings highlight the need for early detection of frailty using clinical scales, which is of vital importance in establishing a prognosis in this population.

Funding

The authors declare that they have not received funding for conducting this study.

Conflicts of interest

The authors declare that they do not have any conflicts of interest. Q6

Acknowledgments

We would like to thank Ms. Claudia Corazza González for her help with the final English-language version.

References

1. Niu S, Tian S, Lou J, Kang X, Zhang L, Lian H, et al. Clinical characteristics of older patients infected with COVID-19: a descriptive study. Arch Gerontol Geriatr. 2020;89:104058, doi:10.1016/j.archger.2020.104058. Epub 2020 Apr 10. PMID: 32339960; PMCID: PMC7194515.
2. Liang SY. Sepsis and other infectious disease emergencies in the elderly. Emerg Med Clin North Am. 2016;34(3):501–22, doi:10.1016/j.emc.2016.04.005. PMID: 27475012; PMCID: PMC502236.
3. Esper AM, Moss M, Lewis CA, Nisbet R, Mannino DM, Martin GS. The role of infection and comorbidity: factors that influence disparities in sepsis. Crit Care Med. 2006;34:2576–82.
4. Lutz M, Arancibia M, Papuzinski C, Stojanova J. Inmunosenescencia, infecciones virales y nutrición: revisión narrativa de la evidencia científica disponible [Immunosenescence, viral infections and nutrition: A narrative review of scientific available evidence]. Rev Esp Geriatr Gerontol. 2022;57(1):33–8, doi:10.1016/j.regg.2021.08.003. Epub 2021 Nov 26. PMID: 34844781.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62, doi:10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. PMID: 32171076.
6. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al., the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323(20):2052–9, doi:10.1001/jama.2020.6775. Erratum in: JAMA. 2020 May 26;323(20):2098. PMID: 32320003.
7. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al., ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985, doi:10.1136/bmj.m1985. PMID: 32444460.
8. Hewitt J, Carter B, McCarthy K, Pearce L, Law J, Wilson FV, et al. Frailty predicts mortality in all emergency surgical admissions regardless of age. An observational study. Age Ageing. 2019;48(3):388–94, doi:10.1093/ageing/afy217. PMID: 30778528.
9. Kastora S, Kounidas G, Perrott S, Carter B, Hewitt J, Myint PK. Clinical frailty scale as a point of care prognostic indicator of mortality in COVID-19: a systematic review and meta-analysis. EClinicalMedicine. 2021;36:100896, doi:10.1016/j.eclinm.2021.100896. PMID: 34036252.
10. Cosco TD, Best J, Davis D, Bryden D, Arkill S, van Oppen J, et al. What is the relationship between validated frailty scores and mortality for adults with COVID-19 in acute hospital care? A systematic review. Age Ageing. 2021;50(3):608–16, doi:10.1093/ageing/afab008. PMID: 33951151.
11. Lewis EG, Breckons M, Lee RP, Dotchin C, Walker R. Rationing care by frailty during the COVID-19 pandemic. Age Ageing. 2021;50(1):7–10, doi:10.1093/ageing/afaa171. PMID: 32725156.
12. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392–7, doi:10.1016/j.jamda.2013.03.022. PMID: 23764209.
13. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health. 2018;3(7):e323–32, doi:10.1016/S2468-2667(18)30091-4. Epub 2018 Jun 14. PMID: 29908859.
14. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol a Biol Sci Med Sci. 2001;56(3):M146–56, doi:10.1093/gerona/56.3.m146. PMID: 11253156.
15. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95, doi:10.1503/cmaj.050051. PMID: 16129869.
16. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging. 2008;12(1):29–37, doi:10.1007/BF02982161. PMID: 18165842.
17. Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health. 2020;5(8):e444–51, doi:10.1016/S2468-2667(20)30146-8. Epub 2020 Jun 30. PMID: 32619408.
18. Dumitrascu F, Branje KE, Hladkowicz ES, Lalu M, McIsaac DI. Association of frailty with outcomes in individuals with COVID-19: a living review and meta-analysis. J Am Geriatr Soc. 2021;69(9):2419–29, doi:10.1111/jgs.17299. Epub 2021 Jun 5. PMID: 34048599.
19. Ramos-Rincón JM, Buonaiuto V, Ricci M, Martín-Carmona J, Paredes-Ruíz D, Calderón-Moreno M, et al., SEMI-COVID-19 Network. Clinical characteristics and risk factors for mortality in very old patients hospitalized with COVID-19 in Spain. J Gerontol Biol Sci Med Sci. 2021;76(3):e28–37, doi:10.1093/gerona/glaa243. PMID: 33103720.
20. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506, doi:10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 30;: PMID: 31986264.
21. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20, doi:10.1056/NEJMoa2002032. Epub 2020 Feb 28. PMID: 32109013.
22. Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, Lumbreras-Bermejo C, Ramos-Rincón JM, Roy-Vallejo E, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry. Rev. Clin. Esp. 2020;220:480–94, doi:10.1016/j.rce.2020.07.003.
23. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:61–5. PMID: 14258950.
24. Rius C, Pérez G, Martínez JM, Bares M, Schiaffino A, Gispert R, et al. An adaptation of Charlson comorbidity index predicted subsequent mortality in a health survey. J Clin Epidemiol. 2004;57(4):403–8, doi:10.1016/j.jclinepi.2003.09.016. Erratum in: J Clin Epidemiol. 2007 Jun;60(6):643. PMID: 15135843.
25. American Psychiatric Association. Neurocognitive Disorders. In: Diagnostic and Statistical Manual of Mental Disorders. fifth edition American Psychiatric Association; 2013.
26. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al., CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12, doi:10.7326/0003-4819-150-9-200905050-00006. Erratum in: Ann Intern Med. 2011 Sep 20;155(6):408. PMID: 19414839.
27. Pranata R, Henrina J, Lim MA, Lawrensia S, Yonas E, Vania R, et al. Clinical frailty scale and mortality in COVID-19: a systematic review and dose-response meta-analysis. Arch Gerontol

Geriatr. 2021;93:104324, doi:10.1016/j.archger.2020.104324. Epub 2020 Dec 15. PMID: 33352430.

28. Brill SE, Jarvis H, Ozcan E, Burns T, Warraich R, Amani L, et al. COVID-19: a retrospective cohort study with focus on the over-80s and hospital-onset disease. medRxiv. 2020;18:194, doi:10.1186/s12916-020-01665-z.
29. Miles A, Webb TE, McLoughlin B, Mannan I, Rather A, Knopp P, et al. Outcomes from COVID-19 across the range of frailty: excess mortality in fitter older people. medRxiv. 2020, doi:10.1101/2020.05.22.20110486.
30. Proietti M, Cesari M. Frailty: what is it? Adv Exp Med Biol. 2020;1216:1–7, doi:10.1007/978-3-030-33330-0_1. PMID: 31894541.
31. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet. 2018;391(10132):1775–82, doi:10.1016/S0140-6736(18)30668-8. Epub 2018 Apr 26. PMID: 29706364; PMCID: PMC5946808.
32. Covid19 Rapid Guideline: Critical Care in Adults. [(accessed on 18 June 2020)]; Available online: http://www.covid19-rapid-guideline-critical-care-in-adults-pdf-66141848681413.pdf Recommendations for the admission of patients with COVID-19 to intensive care and intermediate care units (ICUs and IMCUs) Swiss Med. Wkly. 2020;150:w20227.