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COVID-19 in young and middle-aged adults: predictors of poor outcome and clinical differences

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Abstract

Introduction Young and middle-aged adults are the largest group of patients infected with SARS-CoV-2 and some of them develop severe disease.

Objective To investigate clinical manifestations in adults aged 18–65 years hospitalized for COVID-19 and identify predictors of poor outcome. Secondary objectives: to explore differences compared to the disease in elderly patients and the suitability of the commonly used community-acquired pneumonia prognostic scales in younger populations.

Methods Multicenter prospective registry of consecutive patients hospitalized for COVID-19 pneumonia aged 18–65 years between March and May 2020. We considered a composite outcome of "poor outcome" including intensive care unit admission and/or use of noninvasive ventilation, continuous positive airway pressure or high flow nasal cannula oxygen and/or death.

Results We identified 513 patients < 65 years of age, from a cohort of 993 patients. 102 had poor outcomes (19.8%) and 3.9% died. 78% and 55% of patients with poor outcomes were classified as low risk based on CURB and PSI scores, respectively. A multivariate Cox regression model identified six independent factors associated with poor outcome: heart disease, absence of chest pain or anosmia, low oxygen saturation, high LDH and lymphocyte count < 800/mL.

Conclusions COVID-19 in younger patients carries significant morbidity and differs in some respects from this disease in the elderly. Baseline heart disease is a relevant risk factor, while anosmia and pleuritic pain are associated to better prognosis. Hypoxemia, LDH and lymphocyte count are predictors of poor outcome. We consider that CURB and PSI scores are not suitable criteria for deciding admission in this population.

Keywords COVID-19 · SARS-CoV-2 · Young adults · Mortality

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently causing an unprecedented pandemic of severe respiratory illness, coronavirus disease 2019 (COVID-19), more than 140 million cases having been confirmed around the world by April 2021. It represents a challenge for health systems with extraordinarily high numbers of patients hospitalized with COVID-19 viral pneumonia and more than 3 million deaths [1].

The influence of age on the risk of developing severe pneumonia is stronger with SARS-CoV-2 than with other pathogens, and a large amount of information has been generated on the characteristics of COVID-19 in elderly and very elderly patients [2–4]. In contrast, much less attention has been paid to one of the most worrying aspects of the pandemic, namely, the severity of the disease in some young and middle-aged patients, this being associated with substantial mortality rates and the need for prolonged invasive mechanical ventilation with the resulting sequelae [5].

Moreover, the number of cases of COVID-19 is increasing rapidly among young adults worldwide. The wider use of diagnostic tests has identified that this population group -individuals between 18 and 65-years-old—accounts for 75% of those infected globally, attributable to the fact that they are of working age with high mobility and numerous interpersonal interactions [1].

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A recent cross-sectional survey in various European and American countries showed that under-65-year-olds account for 4–22% of all COVID-19 deaths [6]. Another study described a case-fatality rate ranging from 0.2 to 1.3 in Italy and China in individuals aged 20–60 years at the start of the pandemic [7]. The estimated SARS-CoV-2 infection-fatality rate in the general population during the first wave of the COVID-19 pandemic in Spain in 2020 was between 0.01 and 0.38% in younger age groups (20–60 years)[8].

With the hypothesis that the presentation of COVID-19 pneumonia may be different in young people, we undertook a detailed study of the clinical features, biomarkers and outcomes in the population aged 18–65 years hospitalized for SARS-CoV-2 pneumonia. The main aim was to identify factors predicting risk of clinical deterioration, to escalate the care of at-risk patients. As secondary objectives, we sought to assess potential differences in the characteristics of the disease compared to those in elderly patients, and assess the suitability of the commonly used community-acquired pneumonia (CAP) prognostic scales in this population to facilitate adequate patient care.

For the purpose of this study, we considered a composite outcome of "poor outcome" that included admission to an intensive care unit (ICU) and/or use of noninvasive mechanical ventilation (NIV), continuous positive airway pressure (CPAP), or high flow nasal cannula oxygen (HFNC) therapy and/or death. Similar endpoints have been widely used in other studies [9].

Methods

Study design and population

This was a multicenter observational study based on the analysis of a prospective registry of consecutive patients hospitalized for COVID-19 pneumonia between March 1st and May 31st 2020 in three tertiary medical centers (Cruces University Hospital, La Fe University Hospital and Galdakao-Usansolo University Hospital) in Spain. The study was approved by the local ethics committees in accordance with the Declaration of Helsinki's guidelines for research in humans.

We included consecutive patients aged ≥ 18 years with a new pulmonary infiltrate diagnosed by chest X-ray or computed tomography scan. COVID-19 pneumonia was confirmed by positive reverse transcriptase polymerase chain reaction assay for SARS-CoV-2 in nasopharyngeal swabs.

Patients were excluded if no new pulmonary infiltrates were observed in radiology examinations or if they had previously been hospitalized for COVID-19, as well as if they declined to participate in the study. Pregnant women admitted for delivery were also excluded. We focused on patients aged 18–65-years-old and considered patients ≥ 65 years hospitalized for SARS-CoV-2 pneumonia as the control group for the initial descriptive study.

Data collection

We recorded data on demographic characteristics, medication and baseline comorbidities and Charlson's Comorbidity Index. Heart disease included ischemic or congenital heart disease, congestive heart failure and arrhythmia, while lung disease included asthma, chronic obstructive pulmonary disease and interstitial lung disease. Active cancer was defined as malignancy with treatment ongoing or within the previous 6 months. Patients were considered active smokers when they smoked at least 10 cigarettes per day and heavy alcohol users if they reported a daily alcohol intake of at least 80 g for men or 60 g for women during the previous year. Obesity was defined as a body mass index ≥ 30 kg/m^2. We classified patients as immunocompromised if they were transplant recipients, had hematological malignancies or used systemic steroids, specifically, ≥ 10 mg/day of prednisone for > 3 months or other immunosuppressive treatments.

We also collected data on symptoms, vital signs, laboratory and radiological findings on admission to the emergency department and in-hospital course until discharge or death. To assess the severity of pneumonia on admission, we used the Confusion, Urea nitrogen, Respiratory rate, Blood pressure, age ≥ 65 years (CURB-65) [10] and Pneumonia Severity Index (PSI) scores [11]. Measures of in-hospital clinical course and outcome included: (1) ICU admission; (2) use of invasive mechanical ventilation; (3) use of noninvasive respiratory support or HFNC therapy; (4) in-hospital mortality; and (5) length of hospital stay.

Patients were treated empirically in accordance with current Spanish practice guidelines, based on the Spanish Ministry of Health and the Spanish Agency for Medicine and Health products (AEMPS) in March–April 2020 [12, 13]. In-hospital care was determined by patients' healthcare providers. No interventions were instigated as part of this study.

Study outcome

The primary objective was to compare the baseline comorbidities, and clinical and laboratory data on admission of young and middle-aged patients with and without poor outcome in terms of respiratory function. This composite poor outcome [9] included admission to an ICU and/or use of NIV, CPAP started as an acute treatment in patients without prior home ventilatory support, or HFNC and/or death) with those without complications.

Statistical analysis

Patients hospitalized with COVID-19-related CAP aged ≤ 65 years were considered the study group. Subgroups for comparisons were also formed by dividing this population using the age thresholds of 18–30, 31–50, and 51–64 years.

Continuous variables are reported as the mean (standard deviation) for normally distributed data and otherwise as the median (interquartile range). Categorical variables are presented as frequency (percentage). For the identification of predictors of mortality, a bivariate analysis was performed. Baseline sociodemographic and clinical factors were compared between the two groups using Student's *t* test, in the case of continuous variables that followed a normal distribution or the nonparametric Mann–Whitney *U* test otherwise. The Chi-square test or Fisher's exact test were used for the categorical data. Multivariate analysis was performed using multivariate logistic regression model, including variables with *p*-values lower than 0.100 in the bivariate analysis as predictors. These variables were included in a multivariate logistic regression model in which we eliminated the variables with the highest *p*-values one-by-one until all the variables entered were significant (*p*-value < 0.05). The Hosmer–Lemeshow goodness-of-fit test for logistic regression was used to assess the fit of the model. The predictive ability of the final multivariate model was assessed by area under the receiver operating characteristic (ROC) curve analysis. Differences were considered statistically significant when $p < 0.05$. All analyses were performed using R statistical software (version 4.0.1 R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 513 patients < 65 years, from a cohort of 993 patients hospitalized for SARS-COV2 pneumonia (52% of the total cohort). A considerable number of patients, 102 (19.8%) had a poor outcome, with a mortality rate of 3.9%.

Younger patients vs ≥ 65-year-olds

The main results are summarized in Table 1. All comorbidities were more frequent in the ≥ 65-year-olds except for obesity and smoking. There were no differences between the groups in the percentage of immunocompromised patients. Regarding clinical presentation, the younger patients were more likely to show greater severity, being more likely to have fever, myalgia, digestive symptoms, cough, chest pain and anosmia, though confusion was much less common than in the elderly.

Notably, there were no differences in the radiological presentation at the time of admission. On the other hand, all the laboratory inflammatory markers were lower in the < 65-year-olds (lactate dehydrogenase [LDH], C-reactive protein [CRP], ferritin, and D-dimer) and the lymphocyte and platelet counts were higher in this younger population.

Table 2 summarizes the differences among the age groups regarding the outcomes. There were no differences in rates of ICU admission (14.8 vs 16.6%) or use of invasive ventilation (11 vs 12%), but mortality was notably higher in the elderly (23.5% versus 3.9%; $p < 0.001$).

Comparison between different age groups within patients under 65 years

We formed groups for comparison by dividing the population into the following age groups: 18–30, 31–50 and 51–64 years, containing 17 patients (3.3%), 170 patients (33.1%), and 326 patients (63.5%), respectively. The corresponding rates of poor outcome were: 0%, 13.9%, and 23.3% respectively, the differences being significant; $p < 0.001$. Given that only 17 patients were ≤ 30-years-old, we decided to merge patients between 18 and 50 years into one group for analysis. Results are summarised in Tables 1 and 2. Once again, older patients were found to have more comorbidities except for obesity (although the difference did not reach significance) and higher levels of inflammatory markers. Patients ≤ 50-years-old were less likely to be admitted to ICU (11 vs 19%) and had significantly lower mortality (0.5 vs 5%).

Predictors of "poor outcome" in patients under 65 years

Overall, 102 patients (19.8%) had a poor outcome. The univariate analysis (Table 3) revealed that baseline comorbidities such as heart disease, hypothyroidism and cancer were associated with poor outcome. Baseline treatments were similar in both groups, except for statins. Among the patients with poor outcome, after excluding dyslipidemia, 39% had no comorbidities, 23 of them went to ICU (4% of total young patients) and 5 of them died. There were significant differences in clinical presentation, with more confusion and dyspnea and less anosmia and chest pain in the group with poor outcome.

Regarding the physical examination findings, patients with a poor outcome were more likely to have lower diastolic blood pressure, higher respiratory and heart rates and lower blood oxygen levels. Focusing on laboratory findings, poor outcome was significantly associated with high levels of CRP, ferritin, D dimer and LDH, as well as low lymphocyte and platelet counts.

Table 1 Comparison of baseline characteristics on admission by age

	≥ 65-year-olds $N=480$	< 65-year-olds $N=513$	p value	[18–50] $N=187$	[51–64] $N=326$	p value
Gender (male)	298 (62.1%)	307 (59.8%)	0.511	109 (58.3%)	198 (60.7%)	0.652
Heavy alcohol users	22 (7%)	16 (4.2%)	0.27	5 (3.4%)	11 (4.8%)	0.42
Active smoking	13 (2.8%)	35 (6.9%)	0.005	14 (7.7%)	21 (6.6%)	0.77
Obesity ($n=726$)	130 (34.4%)	148 (42.5%)	0.029	61 (49.2%)	87 (38.8%)	0.079
Hypertension	318 (66.2%)	142 (27.7%)	< 0.001	30 (16.0%)	112 (34.4%)	< 0.001
Diabetes	150 (31.2%)	56 (10.9%)	< 0.001	14 (7.5%)	42 (12.9%)	0.08
Heart disease	140 (29%)	26 (5%)	< 0.001	1 (0.5%)	25 (7.6%)	< 0.001
Lung disease	211 (21.2%)	84 (16%)	< 0.001	30 (16.0%)	54 (16.6%)	0.976
Cancer	49 (7.4%)	8 (2.1%)	< 0.001	11 (0.7%)	7 (3.1%)	0.15
Immunosuppression	20 (3.8%)	30 (5.1%)	0.41	9 (4.2%)	21 (6.4%)	0.37
Comorbidities ≥ 1	451 (94%)	387 (75.4%)	< 0.001	120 (64.2%)	267 (81.9%)	0.001
Charlson's Comorbidity Index, Median (IQR)	1.0 ([0.0–3.0]	0.0 [0–1]	< 0.001	0.0 [0–1]	0.0 [0–1]	0.219
Duration of symptoms, days before admission (Median; IQR)	7 [5–9]	7 [5–10]	0.7	7 [5–9]	7 [6–10]	0.2
Fever	258 (53.8%)	338 (65.9%)	< 0.001	136 (72.7%)	202 (62.0%)	< 0.017
Cough	330 (68.9%)	401 (78.3%)	< 0.001	150 (80.2%)	251 (77.2%)	0.48
Dyspnoea	230 (47.9%)	276 (53.8%)	0.07	114 (61.0%)	162 (49.7%)	0.18
Myalgia	89 (18.6%)	151 (29.4%)	< 0.001	54 (28.9%)	97 (29.8%)	0.91
Confusion	51 (10.6%)	5 (0.9%)	< 0.001	0 (0.0%)	5 (1.5%)	0.16
Chest pain	35 (7.3%)	67 (13.1%)	0.004	33 (17.6%)	34 (10.4%)	0.028
Anosmia	56 (11.7%)	140 (27.3%)	< 0.001	59 (31.6%)	81 (24.8%)	0.124
Digestive symptoms	116 (24.6%)	165 (32.6%)	0.007	65 (35.1%)	100 (31.2%)	0.41
Systolic BP, mmHg (Median; IQR)	130 [115–147]	126 [117–138]	0.014	124 [115–134]	128 [118–141]	0.016
Respiratory rate /min (Median; IQR)	18 [16–24]	18 [16–22]	0.068	18 [16–21]	18 [16–22]	0.393
Heart rate/min (Mean; SD)	88 [16.2]	96.9 [17.3]	< 0.001	99.7 (17.6)	95.3 (16.9)	0.007
SaO2% in room air (Median; IQR)	94 [90–96]	96 [93–97]	< 0.001	96 [94–97]	95 [93–97]	0.008
Glucose, mg/dL (Median; IQR)	119 [106–147]	106 [97–121]	< 0.001	102 [94–114]	109 [99–124]	< 0.001
Urea, mg/dl (Median; IQR)	41 [32–59]	28 [22–36.5]	< 0.001	25 [19–32]	30 [24–38]	< 0.001
LDH, U/L (Median; IQR)	326 [250–414]	281 [232–364]	< 0.001	264 [219–328]	297 [240–382]	< 0.001
CRP, mg/L (Median; IQR)	87 [42–149]	57.5 [26.4–110]	< 0.001	43.8 [20–89.2]	61.7 [31.2–119]	< 0.001
Ferritin, ng/mL (Median; IQR)	776 [308–1317]	589 [292–1086]	0.147	475 [139–823]	671 [367–1187]	0.002
Lymphocyte count/μL (Median; IQR)	880 [620–1200]	1060 [770–1360]	< 0.001	1140 [835–1505]	990 [735–1288]	< 0.001
Platelet count/μL (Median; IQR)	179,000 [140250–242000]	198,000 [154750–247250]	0.001	197,000 [159500–252000]	200,000 [154,000–240,000]	0.613
D-Dimer, ng/mL (Median; IQR)	945 [591–1720]	570 [354–952]	< 0.001	480 [288–785]	633 [419–1050]	< 0.001
CURB score			< 0.001			0.535
0–1	190 (4.0%)	481 (74.2%)		179 (95.7%)	302 (93.2)	
2	204 (43%)	29 (5.6%)		8 (4.2%)	21 (6.4%)	
3–4	80 (16.9%)	1 (0.2%)		0 (0.0%)	1 (0.3%)	

Table 1 (continued)

	≥65-year-olds $N=480$	<65-year-olds $N=513$	p value	[18–50] $N=187$	[51–64] $N=326$	p value
PSI score			<0.001			<0.001
1–2	99 (20.8%)	421 (82.4%)		174 (8%)	247 (76.2%)	
3	168 (35.3%)	52 (10.2%)		11 (5.8%)	41 (12.7%)	
4–5	209 (43.9%)	38 (7.4%)		2 (1.1%)	36 (11.1%)	

BP blood pressure, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *CRP* C-reactive protein

Table 2 In-hospital evolution and outcomes

	≥65-year-olds $N=480$	<65-year-olds $N=513$	p value	[18–50) $N=187$	[51–64] $N=326$	p value
Length of stay, days (Median-IQR)	10 [6.00–19.0]	9 [5–14]	0.003	8 [5–11.5]	9 [5–15]	0.023
HFNC	57 (11.9%)	54 (10.5%)	0.566	13 (6.9%)	41 (12.6%)	0.65
CPAP	22 (4.5%)	7 (1.3%)	0.01	2 (1.0%)	5 (1.5%)	1
Non-invasive ventilation	4 (0.8%)	4 (0.7%)	0.1	1 (0.5%)	3 (0.9%)	0.8
Mechanical ventilation	56 (11.7%)	65 (12.7%)	0.699	17 (9.1%)	48 (14.7%)	0.88
ICU admission	71 (14.8%)	85 (16.6%)	0.495	21 (11.2%)	64 (19.6%)	0.01
Death	113 (23.5%)	20 (3.9%)	<0.001	1 (0.5%)	19 (5.8%)	0.006

HFNC high flow nasal cannula oxygen, *CPAP* continuous positive airway pressure, *ICU* intensive care unit

The median duration of symptoms before admission was 7 days with no significant differences between groups in the multivariate analysis.

Patients with severe respiratory disease did have worse CURB and PSI scores, but 78% of patients with a poor outcome were classified as low risk based on CURB score (0–1) and 55% based on PSI score (1–2).

In the multivariate analysis, six independent factors were found to be associated with clinical deterioration (Table 3): heart disease (OR: 5.41; 95% CI 1.72–16.60; $p=0.003$), chest pain (OR: 0.19; 95% CI 0.03–0.74; $p=0.033$), anosmia (OR: 0.34; 95% CI 0.13–0.76; $p=0.014$), median oxygen saturation (OR: 0.72; 95% CI 0.65–0.80; $p<0.001$), LDH (OR: 1.04; 95% CI 1.01–1.07; $p=0.006$) and lymphocyte count > 800/mL (OR: 0.46; 95% CI 0.24–0.87; $p=0.017$). The Hosmer–Lemeshow goodness-of-fit test for logistic regression gave a p value of 0.6554. In the ROC curve analysis, the area under the curve was 0.88. Figure 1.

Discussion

This multicenter study provides a comprehensive evaluation of host-related factors, process of care and outcome in a consecutive series of young adults hospitalized with SARS-CoV-2 pneumonia. To our knowledge, this is among the largest series published on this topic to date. Our results show that 19.8% of the young patients had a poor outcome, with severe respiratory failure, and 3.9% died. Taken together 18- to 65-year-olds accounted for 52% of all COVID-19 patients admitted to hospital. Our data reveal that a notable proportion of nonelderly patients develop severe disease and confirm that the burden of young and middle-aged adults with COVID-19 hospitalized with severe disease is significant. These findings are consistent with the rates Cunningham et al. found using a national all-payer hospital database in adults aged 18–34 years admitted to US hospitals, namely, 21% required intensive care and 2.7% died [14]. Notably, Altonen et al. reported an even higher mortality rate of 13% in this population in New York City public hospitals [15]. Recent data from the from the Spanish Ministry of Health show that more than 2 million patients between 20 and 60 years of age have been infected with SARS-CoV-2 and 3.9% of them have required hospitalization; 0.39% (10% of hospitalized patients) have been admitted to the ICU with an overall mortality rate of 0.1% [16].

The results of our study illustrate that there are some differences between adults hospitalized for SARS-CoV-2 pneumonia by age. All comorbidities are more frequent in the elderly except obesity and smoking. Obesity is a well-recognized risk factor for severe COVID-19 and death in young patients, probably due to the proinflammatory status associated with abdominal visceral adiposity and a high expression of angiotensin converting enzyme 2 (ACE2) receptors in adipose tissue [17–21]. It should be noted that 60% of the nonelderly patients had at least one comorbidity (and the rate was somewhat higher [70.6%] in those with poor outcomes), some risk factors overlapping with those observed in elderly patients.

Table 3 Predictors of "poor outcome" in patients under 65 years

	All $N=513$	Favorable outcome $N=411$	Poor outcome $N=102$		Multivariate analysis	
					OR (95% CI)	p value
Gender (male)	307 (59.8%)	230 (56.0%)	77 (75.5%)			
Age, years				0.008		
18–30	17 (3.3%)	17 (4.1%)	0 (0.0%)			
31–50	170 (33.1%)	144 (35.0%)	26 (25.5%)			
50–65	326 (63.5%)	250 (60.8%)	76 (74.5%)			
Smoking	35 (6.9%)	29 (7.2%)	6 (6.12%)	0.878		
Comorbidities ≥ 1 (excluding dyslipidemia)	309 (60.2%)	237(57.5%)	72 (70.6%)	0.023		
Charlson's Comorbidity Index (Median-IQR)	0.0 (0.00–1.00)	0.0 (0.00–1.00)	0.0 (0.00–1.00)	0.291		
Obesity ($N=348$)	148 (42.5%)	117 (42.2%)	31 (43.7%)	0.935		
Hypertension	142 (27.7%)	107 (26.0%)	35 (34.3%)	0.121		
Diabetes	56 (10.9%)	44 (10.7%)	12 (11.8%)	0.897		
Dyslipidemia	142 (27.7%)	107 (26.0%)	35 (34.3%)	0.121		
Heart disease	26 (5.0%)	13 (3.1%)	13 (12.7%)	<0.001	5.41 (01.72, 16.6)	0.003
Chronic kidney disease ($N=373$)	15 (4.0%)	10 (3.3%)	5 (6.9%)	0.180		
Lung disease	84 (16.4%)	66 (16.1%)	18 (17.6%)	0.811		
Peripheral vascular disease	8 (1.5%)	6 (1.4%)	2 (1.9%)	0.662		
Malignancy	8 (2.1%)	4 (1.3%)	4 (5.5%)	0.048		
Hypothyroidism ($N=321$)	24 (7.4%)	24 (9.4%)	0 (0.0%)	0.006		
Immunosuppression	30 (5.1%)	22 (5.3%)	8 (7.8%)	0.493		
ACE inhibitors	107 (20.9%)	81 (19.7%)	26 (25.5%)	0.250		
Statins	97 (18.9%)	70 (17.0%)	27 (26.5%)	0.042		
Corticoids						
None	456 (88.9%)	362 (88.1%)	94 (92.2%)	0.403		
Inhaled	43 (8.3%)	38 (9.2%)	5 (4.9%)			
Oral	14 (2.7%)	11 (2.6%)	3 (2.9%)			
Duration of symptoms (days) before admission Median (IQR)	7 [5–10]	7 [6–10]	7 [5–8]	<0.001		
Fever	338 (65.9%)	263 (64.0%)	75 (73.5%)	0.089		
Cough	401 (78.3%)	319 (77.8%)	82 (80.4%)	0.665		
Dyspnoea	276 (53.8%)	207 (50.4%)	69 (67.6%)	0.003		
Myalgia	151 (29.4%)	125 (30.4%)	26 (25.5%)	0.392		
Confusion	5 (0.9%)	1 (0.2%)	4 (3.9%)	0.006		
Chest pain	67 (13.1%)	60 (14.6%)	7 (6.8%)	0.056	0.19 (0.03, 0.74)	0.033
Anosmia	140 (27.3%)	140 (27.3%)	14 (13.7%)	0.001	0.34 (0.13, 0.76)	0.014
Digestive symptoms	165 (32.6%)	138 (34.2%)	27 (26.5%)	0.173		
Systolic BP, mmHg (Median-IQR)	126 [117–138]	126 [118–138]	124 [115–135]	0.301		
Respiratory rate /min (Median-IQR)	18.0 [16–22]	17.0 [16–20]	24.0 [19–32]	<0.001		
Heart rate/min (Mean;SD)	96.9 (17.3)	96.5 (16.9)	98.7 (18.7)	0.293		

Table 3 (continued)

	All $N=513$	Favorable outcome $N=411$	Poor outcome $N=102$		Multivariate analysis	
					OR (95% CI)	p value
SaO2% in room air on admission (Median-IQR)	96 [93–97]	96 [94–97]	91 [85–95]	<0.001	0.72 (0.66, 0.80)	<0.001
Bilateral infiltrates	370 (72.1%)	281 (68.4%)	89 (87.3%)	<0.001		
Glucose, mg/dL (Median-IQR)	106 [97–121]	104 [96–119]	116 [103–138]	<0.001		
Urea, mg/dL (Median-IQR)	28 [22–36]	27 [22–34]	33 [24–45]	<0.001		
ALT U/L (Median-IQR)	31.0 [20–47]	30 [19–47]	34 [22.5–53.5]	0.025		
LDH U/L (Median-IQR)*	28.1 [23.2;36.4]	26.7 [22.4;33.3]	39.4 [29.1;49.5]	<0.001	1.04 (1.01, 1.07)	0.006
CRP mg/L (Median-IQR)	57.5 [26.4–110]	48.4 [23.6–92.4]	107 [62.2–150]	<0.001		
Ferritin, ng/mL (Median-IQR)	589 [292–1086]	564 [262–946]	1062 [551–1985]	<0.001		
Lymphocyte count > 800/μL	360 (70.2%)	303 (73.7%)	57 (55.9%)	<0.001	0.46 (0.24–0.87)	0.017
Platelet count/μL (Median-IQR)	198,000 [154,000–247,250]	203,000 [160,000–251,750]	175,000 [139,000–224,750]	0.001		
D-Dimer, ng/mL (Median-IQR)	570 [354–952]	540 [340–875]	824 [480–1300]	<0.001		
Length of stay (days) (Median-IQR)	9 [5–14]	7 [5–10]	24.0 [15–41.8]	<0.001		
CURB score				<0.001		
0–1	481 (94.2%)	401 (98.1%)	90 (78.5.0%)			
2	29 (5.68%)	8 (1.96%)	21 (20.6%)			
3–4	1 (0.20%)	0 (0.00%)	1 (0.98%)			
PSI score				<0.001		
1–2	421 (82.4%)	364 (89%)	57 (55.8%)			
3	52 (10.2%)	34 (8.31%)	18 (17.6%)			
4–5	38 (7.44%)	11 (2.69%)	27 (26.4%)			
HFNC	54 (10.5%)	0	54 (10.5%)			
CPAP	7 (1.3%)	0	7 (1.3%)			
Non-invasive ventilation	4 (0.7%)	0	4 (0.7%)			
Mechanical ventilation	65 (12.7%)	0	65 (12.7%)			
ICU admission	85 (16.6%)	0	85 (16.6%)			
Death	20 (3.9%)	0	20 (3.9%)			

BP blood pressure, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase *LDH is presented for every 10 unit increase, *CRP* C-reactive protein, *OR* odds ratio, *CI* confidence interval

Area under the receiver operating characteristic curve (95% CI) = 0.88

Hosmer–Lemeshow p value = 0.655

There are also several differences in clinical presentation. Patients under 65 years of age are more symptomatic, in particular, more often having fever, chest pain, myalgia and especially anosmia, likely a consequence of a stronger immune response. Conversely, confusion is very rare in younger patients. All laboratory parameters are worse in the elderly population. Some of these findings have been observed previously in retrospective research [22].

Though the rates of intubation, respiratory support or HFNC are similar in the two groups, there are clear differences in the mortality rate (3.9% vs 23.5%). Many elderly patients died without being intubated. On the other hand, young patients who received mechanical ventilation had a better prognosis, probably because of the age effect on functional reserve and ability to recover.

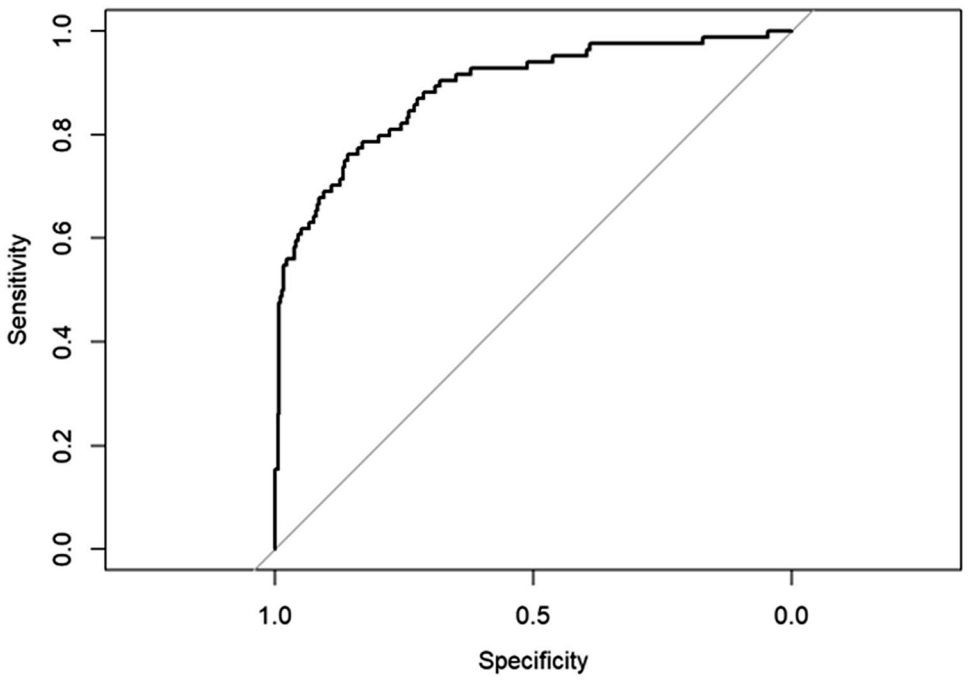

Fig. 1 Area under the curve (ROC) multivariate logistic regression of factors associated with poor evolution in patients aged 18–65. Area under the curve: 0.886

For the purpose of our analysis, we define "poor outcome" as a composite index that included ICU admission and/or use of CPAP, noninvasive ventilation, HFNC or death. Although ICU admission may be subjective, in high pressure conditions as in the first wave in Spain, only those who really needed it were admitted to the ICU, as shown by the fact that 92% of them needed mechanical ventilation or HFNC.

The multivariate analysis identified six factors associated with poor outcome patients under 65 years of age. All these can be assessed based on data available on admission and could help to determine the initial site and intensity of care. The only baseline comorbidity that carried a significant risk in our study was heart disease. Numerous studies have shown that patients with underlying heart diseases have higher odds of death from COVID-19 [23–26] and it has also been described as a risk factor in a younger population [15]. The worse prognosis of COVID-19 in patients with a history of heart disease could be related to elevated expression of ACE2 and a higher baseline production and release of renin. Heart disease in populations with a low prevalence of that type of comorbidity, such as non-elderly patients, behaves as a major risk factor for poor outcome and should be considered when evaluating young patients with COVID-19 and might also be a justification for prioritizing vaccination or future preventive therapies.

Regarding clinical symptoms affecting younger patients, pleuritic pain is associated with a better outcome. This has been previously reported as an independent prognostic factor in patients with CAP and bacteremia. Although the reason for this remains unclear, it has been suggested that it may be because these patients seek medical attention earlier or that pain reflects a stronger immune response [27–29].

The second clinical feature that was significant in the multivariate analysis is anosmia, one of the most characteristic symptoms of COVID-19, and present in 27% of our under-65-year-old patients. In some previous studies, it has been associated with a lower odds of severe coronavirus disease and death. This might be related to a different inflammatory profile with a better local immune response, which could limit the spread of the virus in the body resulting in less severe disease but also a stronger local inflammatory response that could affect olfactory cells [30–32].

Oxygen saturation is the finding from the examination at admission that was most significant in the multivariate analysis. In this sense, our study confirms previously published results, a recent systematic evaluation of 22 prognostic models concluding that baseline oxygen saturation in room air is the strongest predictor of deterioration [9]. The measurement of oxygen saturation could provide an opportunity for innovation and telemedicine in this younger population.

We identified lymphocyte count and LDH level as significant laboratory variables in the multivariate analysis. To date, almost 100 different predictive models with sophisticated statistical models and some systematic reviews have been published on COVID prognosis. Our results are generally in line with these studies, LDH level and lymphocyte count being included in most of the models, although they have not been focused on adults under 65-years-old [26, 33–36]. LDH is expressed extensively in body tissues, including the lungs and it is released during tissue damage, indicating the extent of the disease.

In a recent meta-analysis, LDH > 250 U/L was associated with poor prognosis [37]. Early in the pandemic, lymphopenia was recognized as a useful marker of progression and severe coronavirus disease. Lymphocytes express the ACE2 receptor of the virus and could be a target for the virus. Apoptosis or functional exhaustion of cytotoxic lymphocytes as a response to hyperinflammation has also been proposed as an explanation for the depletion of lymphocytes [38].

Finally, one of the main conclusions of our study is the poor performance of the traditional scores for outpatient treatment of CAP, namely, PSI and CURB in this population ≤ 65-years-old with COVID pneumonia. As many as 78% of our young and middle-aged patients with poor outcome would have been classified as low risk based on their CURB score (0–1) and 55.8% based on their PSI score (1–2). There is much controversy regarding this topic with little agreement but clearly CURB and PSI scores underestimate severity in young COVID-19 patients and should not be used. This lack of accuracy could be because these scores do not consider inflammatory response parameters which play an important role in the pathogenesis of COVID-19 with an excessive production of proinflammatory cytokines, the so-called cytokine storm. CURB score does not include hypoxemia either, and severe COVID-19 is characterized by severe respiratory insufficiency [39, 40].

There are several limitations in our study. First, some anthropometric data were missing especially in patients who went directly to the ICU and died, this explaining the non-significance of obesity as a risk factor for poor outcome in our patients. Second, data were collected between March and May, during the first wave of COVID and medical treatments, ventilatory support practices and also the COVID stains have changed since then and hence the outcomes might be different now. Third, it is an observational study and treatment strategies were not uniform across hospitals or over time. Unfortunately, a definitive effective treatment has yet to be identified. Fourth, the number of young patients with comorbidities is surprisingly high and this could have affected the results and introduced bias.

To conclude, our results show that COVID-19 is associated with significant morbidity in younger patients and underline the importance of infection prevention measures in this active and working-age group, especially in the presence of comorbidities. COVID-19 in under-65-year-olds differs in some respects from this disease in elderly populations, with heart disease being an important risk factor, anosmia and pleuritic pain more frequent and associated to better prognosis, and hypoxemia, high LDH and low lymphocyte count as predictors of a poor outcome. We consider that low CURB or PSI scores are not suitable criteria for recommending outpatient management in this population.

Author contributions ETH and LAR take the responsibility of the manuscript as a whole. ETH, LAR, RZJ, RMV, RMO and PPE conceived and designed the study. AUE, PGH, PGJ, RMO, and LAR enrolled patients and collected and compiled data. BSZ performed the statistical analysis. ETH, RZJ, LAR, RMO, ATM, PPE, and RMV analyzed and interpreted the data. ETH, RZJ, LSF and LAR wrote the manuscript. RMV, RMO, ATM, AUE and PPE commented and revised the report. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Biomedical Research Ethics Committee of Euskadi (PI2020-083) approved this study.

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