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Infectious Medicine 1 (2022) 81–87

Contents lists available at ScienceDirect

Infectious Medicine

journal homepage: www.elsevier.com/locate/imj

Original Article

Clinical characteristics of COVID-19 hospitalized patients associated with mortality: A cohort study in Spain

Manuel Lozano[a,b,*], Adina Iftimi[c], Alvaro Briz-Redon[d], Juanjo Peiró[c], Lara Manyes[a], María Otero[e], Mayte Ballester[e], M. Dolores de las Marinas[f], Juan Carlos Catalá[e], José de Andrés[e,g], Carolina Romero[e,h]

[a] Preventive Medicine and Public Health, Food Sciences, Toxicology and Forensic Medicine Department, Universitat de València, Valencia, Spain
[b] Epidemiology and Environmental Health Joint Research Unit, FISABIO–Universitat Jaume I–Universitat de València, Valencia, Spain
[c] Department of Statistics and Operations Research, University of Valencia, Valencia, Spain
[d] Statistics Office, City Council of Valencia, Valencia, Spain
[e] Department of Anesthesia, Critical Care and Pain Unit, University General Hospital, Valencia, Spain
[f] Division of Allergy and Immunology, University General Hospital, Valencia, Spain
[g] Anesthesia Unit-Surgical Specialties Department, Valencia University Medical School, Valencia, Spain
[h] Division of Research Methodology, European University, Valencia, Spain

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Respiratory insufficiency
Mortality
Proportional hazard model
Pandemics
Coronavirus infections
Epidemiology

ABSTRACT

Background: The heterogeneity of patients with COVID-19 may explain the wide variation of mortality rate due to the population characteristics, presence of comorbidities and clinical manifestations.
Methods: In this study, we analyzed 5342 patients' recordings and selected a cohort of 177 hospitalized patients with a poor prognosis at an early stage. We assessed during 6 months their symptomatology, coexisting health conditions, clinical measures and health assistance related to mortality. Multiple Cox proportional hazards models were built to identify the associated factors with mortality risk.
Results: We observed that cough and kidney failure triplicate the mortality risk and both bilirubin levels and oncologic condition are shown as the most associated with the demise, increasing in four and ten times the risk, respectively. Other clinical characteristics such as fever, diabetes mellitus, breathing frequency, neutrophil-lymphocyte ratio, oxygen saturation, and troponin levels, were also related to mortality risk of in-hospital death.
Conclusions: The present study shows that some symptomatology, comorbidities and clinical measures could be the target of prevention tools to improve survival rates.

1. Introduction

Since the outbreak of coronavirus disease (COVID-19) began in December 2019, more than 149 million people have developed SARS-CoV-2 infection, and more than 3 million have died worldwide. In Spain, by mid-2021 up to 3.5 million cases were reported causing more than 77,000 deaths [1].

There are several studies describing the clinical characteristics and outcomes of hospitalized patients with SARS-CoV-2. The heterogeneity of patients treated in China [2], Italy [3], UK [4], USA [5–7] or Spain [8–10] may explain the wide variation of mortality rate due to the population characteristics, presence of comorbidities and clinical manifestations.

The first confirmed case of COVID-19 in Valencia, Spain, was reported on February 19, 2020. The Consorcio Hospital General Universitario de Valencia (CHGUV), that assists approximately 364,000 patients, was designated as a COVID-19 center and described an infection rate with a heterogeneous distribution during the following 6 months. In this study, we analyze the

* Corresponding author.
E-mail address: manuel.lozano@uv.es (M. Lozano).

https://doi.org/10.1016/j.imj.2022.04.002
Received 9 December 2021; Received in revised form 25 March 2022; Accepted 17 April 2022

symptomatology, coexisting health conditions, clinical measures and health assistance, in a selected cohort of patients with a poor prognosis at an early stage in hospitalized patients from Valencia during this period and assess the clinical characteristics associated with mortality.

2. Materials and Methods

2.1 Study population

This observational prospective study was conducted at the Consorcio Hospital General Universitario of Valencia (CHGUV), an academic public hospital that serves the largest area in the city, consisting of approximately 364,000 patients. The study was approved by the institutional review board, and the requirement for informed consent was waived. All consecutive patients who were tested for COVID-19 were included from February 19 to August 31, 2020. A total of 5342 patients were treated during this period and 177 COVID-19 positive adults confirmed by PCR, admitted to the hospital due to clinical complications, with a World Health Organization ordinal scale 4 (oxygen by masque or nasal prongs) or 5 (noninvasive ventilation or high-flow oxygen) [11], and followed up until recovery or death, were selected. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12].

2.2 Data collection

Data collected included patient demographics (residence, biological sex, and age, in years); treatment reason (symptomatology, contact or other, categorized as yes/no); the recorded symptomatology during the observation period (yes, no) such as fever, asthenia, altered consciousness, headache, myalgia, arthralgia, eczema, nasal congestion, anosmia, sore throat, dyspnea, cough, expectoration, pleuritic pain, hemoptysis, diarrhea, and nausea; intensive care admission (yes, no); presence of smoking habit (current, former or no smoker) and pregnancy (yes, no); comorbidities (yes, no) such as hypertension, cardiovascular disease, diabetes mellitus, obesity, chronic obstructive pulmonary disease, asthma, oncological process, immunosuppression, stroke, kidney and liver failure, and deep vein or pulmonary thrombosis; as well as laboratory tests and clinical characteristics, including mean arterial blood pressure (mmHg), cardiac frequency (beats/minute), oxygen saturation (%), breathing frequency (breaths/minute), lymphocytes (units/μL), neutrophil lymphocyte ratio, platelets (units/μL), D-dimer (ng/mL), activated partial thromboplastin time (seconds), international normalized ratio, fibrinogen (mg/dL), bilirubin (mg/dL), lactic acid dehydrogenase (units/L), ferritin (ng/mL), creatinine (mg/dL), and troponin (ng/L). Outcomes observed were the length of stay until recovery or death. Clinical examinations included chest radiography if necessary (unilobar, multilobar, clean or not performed).

2.3 Statistical analyses

Basic descriptive statistics were calculated for each collected covariate. Death in the whole sample was categorized (death status: yes, no) to run survival analyses as time-dependent response variable. Demographic information, symptomatology, intensive care admission, smoking habit, pregnancy, comorbidities, and radiography results were considered as predictive covariates. Kaplan–Meier survival curves were estimated to compare the survival during the observation period, overall, and stratified for sex and age range (20–50 years (n = 25); 51–60 years (n = 22); 61–70 years (n = 31); 71–80 years (n = 47); and ≥81 years (n = 52)). Simple Cox proportional hazards models were used to control sex and age as confounders, considering each covariate as predictive variable, with and without sex and age adjustment (Table S1). Multiple Cox proportional hazards models were built to identify the associated covariates with mortality risk. All multiple models were adjusted for sex and age. Each multiple model was built following three steps: 1) Obtaining a first multiple basal model by using all the symptomatology covariates previously associated with a p-value <0.2 in the simple analyses. Following a backward elimination procedure, all the symptomatology covariates associated with the mortality risk at a p-value level <0.1 in the likelihood ratio test were retained in the model; 2) comorbidities were added to this clinical symptomatology basal model individually and those with a p-value <0.2 were candidates to enter in the model. Following a backward elimination procedure, all these comorbidities candidate covariates associated with the mortality risk at a p-value level <0.1 were retained in the model; 3) The same procedure was repeated on the clinical symptomatology and comorbidities basal model using clinical covariates in order to obtain the final multiple model. Statistical analysis was carried out using R statistical software version 3.5.1 [13]. Kaplan–Meier curves were plotted and Cox regressions built by using the *survival* R package [13]. The final multiple model was validated by means of proportional hazards assumption testing based on weighted residuals [14] by using the *cox.zph* function. Influential outliers were assessed observing beta deviations with *ggcoxdiagnostics* function of *survminer* package [15]. Nonlinearity was evaluated plotting the Martingale residuals and natural cubic splines with one or two internal knots were compared through Akaike (AIC) scores. Then, the lowest AIC nonlinear model and linear model were compared using graphical examination and the Likelihood Ratio test.

Significance level <0.05 was considered in all tests, although marginally significant effects (p-value <0.1) were also considered.

3. Results

Descriptive statistics of the study variables are displayed in Table 1. From all the Hospital COVID-19 patients (n = 5342), 177 were selected (3.3%). A total of 52 patients (27.4%) died in a time period (mean ± SD) of 18 (33.7) days. These non-survivors were 78.5 ± 11.1 years old, significantly older than survivors (66.3 ± 15.9 years, Wilcoxon test p-value <0.001). Differences regarding sex were not observed (Log-Rank test p-value = 0.400) but higher mortality risk was observed with increasing age (p = 0.009) (Supplemental Fig. S1). Almost 35% of patients who died were admitted in the intensive care unit during the observation period. Main symptomatology recorded among non-survivors was asthenia (Fisher's test p-value = 0.022), altered consciousness (p <0.001), eczema (p = 0.082), and dyspnea (p = 0.001). Some coexisting conditions were associated with mortality, such as cardiovascular disease (p = 0.019), diabetes mellitus (p = 0.011), oncologic process (p = 0.030), stroke (p = 0.007), and kidney failure (p = 0.001). Clinical variables related to non-survivors were lower mean arterial blood pressure (Wilcoxon test p-value = 0.084), oxygen saturation (p <0.001), and lymphocytes count (p = 0.011), as well as higher breathing frequency (p = 0.005), D-dimer (p = 0.011), activated partial thromboplastin time p = (0.056), neutrophil lymphocyte and international normalized ratios, bilirubin, lactic acid dehydrogenase and troponin (p <0.001), ferritin (p = 0.071), and creatinine (p = 0.003). Performed thoracic X-rays showed multilobar outcome more frequently among non-survivors.

Simple Cox proportional hazards models, considering each covariate as predictive variable, did not indicate differences between models with and without sex and age adjustment (Supplemental Table S1). Multiple Cox proportional hazards model showed higher mortality risk with increasing age (hazards ratio HR [95% confidence in terval] = 1.06 [1.02–1.11]), the intensive care admission 5.27 [2.35–11.81], the presence of cough (2.61 [1.10–6.21], diabetes mellitus (1.73 [0.92–3.25], and oncologic condition (10.13 [4.06–25.24], as well as higher breathing frequency (1.06 [1.02–1.10], neutrophil lymphocyte ratio (1.01 [1.00–1.02], and troponin levels (1.00 [1.00–1.01]). Inverse relationships were found with fever (0.32 [0.16–0.66]) and marginally with oxygen saturation (0.97 [0.94–1.00]) (Fig. 1). The multiple Cox proportional hazards model passed the proportional hazards assumption (weighted least-squares test for the global model p-value = 0.197) (Supplemental Fig. S2). Comparing the magnitudes of the largest beta values to the regression coefficients suggested that none of the observations were influential individually (Supplemental Fig. S3). Linear model fitted better than nonlinear multiple Cox proportional hazards model (AIC = 408.31 and 418.79, respectively) and any variable showed associations in nonlinear terms (results not shown). Kaplan–Meier curves stratifying by each significant covariate are shown in Supplemental Figures S4 to S17 (continuous covariates were categorized as binary by median cut-off).

4. Discussion

The COVID-19 pandemic outbreak is an ongoing crisis that is causing global uncertainty. This pandemic has become a health threat to the general population and healthcare workers worldwide, with uncertainty about new strains and its new unknown epidemiological factors. Given the high rate of transmission of the infection among humans, it is important to recognize the basis of its pathogenicity, mortality, and related clinical characteristics, which can lead to the discovery of effective treatments and prevention tools.

In this Spanish cohort study, we assessed the relationship between the symptomatology, coexisting health conditions, clinical measures and health assistance, and mortality risk in a screening sample from COVID-19 positive adults with oxygen by masque, nasal prongs, noninvasive ventilation or high-flow oxygen, and followed until recovery (70.6%) or death (29.4%). Factors such as age and some clinical characteristics seem to play a role in this relationship. Overall, multiple model showed that patients who presented cough, specific comorbidities like diabetes mellitus, kidney failure and an oncologic process, as well as higher breathing frequency, neutrophil lymphocyte ratio and troponin levels, were related to an increased risk of in-hospital death. However, fever and oxygen saturation were associated with lower mortality risk. A relevant fact that has been elucidated in our results is the increased morbimortality detected in COVID-19 positive patients with chronic kidney disease almost tripled the mortality in our sample [16]. Perhaps creatinine could be a marker indicating the degree of severity of COVID-19 inpatients or perhaps it could be due to a possible direct involvement of the kidney by this coronavirus [17]. Until now, some authors have also established increased mortality in patients admitted for COVID-19 and those who developed acute kidney injury during the hospital stay [18].

The clinical characteristics of COVID-19 occur across a broad spectrum, ranging from asymptomatic infection to severe respiratory failure [19,20]. The main symptoms include fever, cough, myalgia, and dyspnea [19,20]. Headache, diarrhea, fatigue, sore throat, anosmia, ageusia, chest pain, hemoptysis, sputum production, rhinorrhea, nausea, vomiting, skin rash, impaired consciousness, and seizure have been also observed [19–21], but

Table 1
Descriptive statistics of study population screening.

	Targeted testing	Population screening			
	All patients	All persons	Survivors	Non-survivors	*p*-value*
Sample size (n)	5342	177	125	52	
SARS-CoV-2 PCR positivity (% negative)	20.6	0	0	0	
Sex (% male)	46	56.5	54.4	61.5	0.410
Age (mean±SD years)	45.3 (22.5)	69.9 (15.7)	66.3 (15.9)	78.5 (11.1)	<0.001
Death (% yes)	3.7	29.4			
Days from positivity until death (mean ± SD days)	41.2 (47.2)			18.0 (33.7)	
Treatment reason (%)					
Symptomatology		84.0	84.0	90.4	0.590
Contact		12.0	12.0	7.7	
Other		4.0	4.0	1.9	
Intensive care unit admission (% yes)		17.5	10.4	34.6	<0.001
Symptomatology (% yes)					
Fever		75.7	80.0	65.4	0.054
Asthenia		68.4	63.2	80.8	0.022
Altered consciousness		22.6	13.6	44.2	<0.001
Headache		33.3	31.2	38.5	0.384
Myalgia / Arthralgia		41.2	40.0	44.2	0.619
Eczema		9.0	6.4	15.4	0.082
Nasal congestion		26.6	23.2	34.6	0.136
Anosmia		27.7	26.4	30.8	0.583
Sore throat		26.0	26.4	25.0	0.999
Dyspnea		53.7	45.6	73.1	0.001
Cough		73.4	70.4	80.8	0.192
Expectoration		27.1	24.0	34.6	0.193
Pleuritic pain		17.5	18.4	15.4	0.828
Hemoptysis		11.3	9.6	15.4	0.301
Diarrhea / Nausea		32.2	32.0	32.7	0.999
Coexisting conditions (% yes)					
Current smoker		10.2	8.0	15.4	0.999
Former smoker		23.7	24.8	21.2	0.999
Hypertension		52.0	48.0	61.5	0.137
Cardiovascular disease		29.4	24.0	42.3	0.019
Diabetes mellitus		29.9	24.0	44.2	0.011
Obesity		22.0	19.2	28.8	0.168
Chronic obstructive pulmonary disease		14.7	12.8	19.2	0.351
Asthma		6.8	7.2	5.8	0.999
Oncologic condition		10.7	7.2	19.2	0.030
Immunosuppressed condition		8.5	6.4	13.5	0.143
Stroke		30.5	24.0	46.2	0.007
Kidney failure		11.9	6.4	25.0	0.001
Liver failure		2.3	2.4	1.9	0.999
Pregnancy		0.6	0.0	1.9	0.294
Deep vein / Pulmonary thrombosis		2.3	2.4	1.9	0.999
Clinical variables (mean±SD)					
Mean arterial blood pressure (mm Hg)		94.5 (15.6)	95.8 (14.1)	91.3 (18.5)	0.084
Cardiac frequency (beats/minute)		87.3 (18.4)	86.6 (17.4)	90.3 (20.6)	0.194
Oxygen saturation (%)		91.1 (10.3)	93.1 (9.6)	86.0 (10.1)	<0.001
Breathing frequency (breaths/minute)		22.4 (8.8)	20.9 (7.3)	26.0 (10.9)	0.005
Lymphocytes (units/μL)		1141.8 (1224.0)	1167.2 (1084.6)	1080.8 (1518.0)	0.011
Neutrophil lymphocyte ratio		8.6 (15.0)	5.8 (5.7)	15.3 (25.3)	<0.001
Platelets (units/μL)		185,374.8 (83,337.2)	188,405.1 (83,825.2)	178,090.4 (82,500.4)	0.558
D-dimer (ng/mL)		864.3 (1093.0)	726.5 (851.3)	1195.5 (1484.1)	0.011
Activated partial thromboplastin time (seconds)		30.2 (8.6)	29.1 (6.7)	32.9 (11.6)	0.056
International Normalized Ratio		1.4 (1.7)	1.1 (0.2)	1.99 (2.99)	<0.001
Fibrinogen (mg/dL)		589.3 (85.9)	574.0 (86.8)	626.0 (72.3)	<0.001
Bilirubin (mg/dL)		0.8 (0.4)	0.7 (0.3)	0.9 (0.5)	<0.001
Lactic acid dehydrogenase (units/L)		557.7 (255.7)	510.7 (211.9)	670.6 (313.2)	<0.001
Ferritin (ng/mL)		669.3 (559.9)	596.0 (456.0)	845.3 (729.0)	0.071
Creatinine (mg/dL)		1.0 (0.8)	0.9 (0.4)	1.4 (1.2)	0.003
Troponin (ng/L)		38.4 (100.3)	18.5 (47.6)	86.3 (160.9)	<0.001
Thoracic X-rays (% yes)					
Unilobar		35.6	44.0	15.4	<0.001
Multilobar		40.7	36.0	51.9	
Clean		19.8	19.2	21.2	
Not performed		4.0	0.8	11.5	

* Fisher's Exact Test for Count Data; Wilcoxon rank sum test with continuity correction for continuous data.

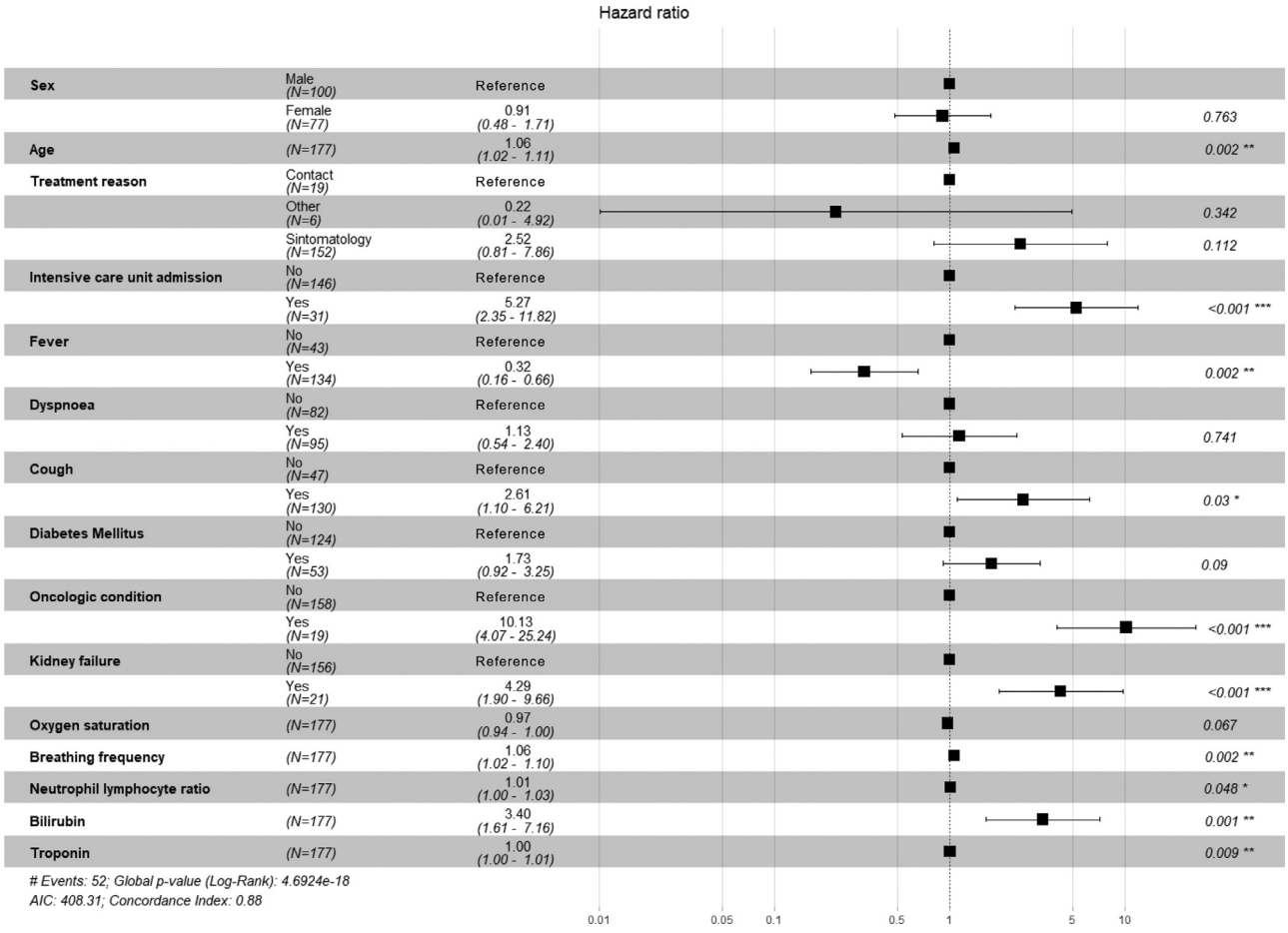

Fig. 1. Forest plot of estimated effects of symptomatology, coexisting health conditions, clinical measures and health assistance on mortality risk, in the multiple Cox proportional hazards model ($n = 177$).

most severe are usually older patients showing dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, some comorbidities (hypertension, diabetes mellitus, and cardiovascular disease), and abnormal chest imaging findings [22,23]. The fact that the variable disorientation was statistically significant in our results, may be due in part to the fact that the most severe patients had increased breathing effort associated with hypoxemia. This circumstance in turn corresponds to hypercapnia, which is a known contributing factor to disorientation and impairment of baseline neurological status.

Previous research about the clinical characteristics in demised COVID-19 patients is inconclusive. This fact may be explained by the heterogeneous affected population, health assistance systems and different virus strains coexisting in time. According to a meta-analysis carried out in 2401 deceased patients [24], common symptoms in non-survivors included fever (70.6%–100%), dyspnea (38.89%–85.7%), cough (22.4%–78%), fatigue (22%–61.9%), and relevant comorbidities such as hypertension, chronic cardiovascular disease, diabetes mellitus, and chronic cerebrovascular disease. Compared with the surviving COVID-19 patients, the deceased had lower platelet levels and higher C-reactive protein and lactate dehydrogenase at admission, which have not been shown significant in the multiple model of the present study. These results are supported by another wide meta-analysis performed in 34 studies with 5057 patients [25]. However, this second study also observed lymphopenia among dead patients (50.1%, 95% CI 38.0%–62.4%), which has been shown to be associated with mortality in our study.

On the other hand, other studies performed in COVID-19 non-survivors do show other coincident results with the present study. From a large Chinese study carried out in 1099 patients with laboratory-confirmed COVID-19, 67 died with fever and cough as the most common symptoms and lymphocytopenia was shown in 83.2% of them [19]. Lymphocytes decrease has been shown as the common clinical factor associated to an increased mortality risk in other studies [9,26–28]. Several studies have found that tobacco smoke is a protective factor and that it influences the clinical course of patients affected by COVID-19 by decreasing the severity of the manifestations [29–31]. However, in our sample, we didn't find any relevant role for tobacco smoke and clinical severity.

To date, three large Spanish studies have been found assessing the associated factors with mortality risk. One

of them reported the first 1255 adult cases in Madrid and also carried out multiple Cox models, observing some similar results regarding older age (HR 1.07, 95% CI 1.06–1.09), diabetes mellitus (HR 1.45, 95% CI 1.09–1.92), and lymphocytopenia (HR 1.62, 95% CI 1.20–2.20) [9]. The second one was also performed in Madrid in 1,828 patients during the same period with a fatality rate of 14.6%, although no associated factors to survival were assessed [10]. A third observational multicenter study described clinical characteristics of very old patients (≥80 years old) in 150 Spanish hospitals (2772 patients), observing similar associations between higher mortality risk and diabetes mellitus (25.6% of cases), oxygen saturation (<90%), unilateral-bilateral infiltrates on chest x-rays, neutrophils ($\geq 7.5 \times 10^3$ /μL), and lymphocytes ($<0.8 \times 10^3$ /μL). However, higher fever was related to an increased mortality risk by using logistic regressions [28].

Lymphocytopenia has been one of the most common clinical characteristic associated with COVID-19 patient's mortality across studies. An explanation for the relationship between the virus and the lower lymphocytes levels has been proposed by means of immune responses activation, which may overproduce proinflammatory cytokines, causing uncontrolled inflammatory responses in patients with severe COVID-19. This condition may lead to lymphopenia and lymphocyte dysfunction [32]. Among comorbidities, diabetes mellitus has been shown to be reiterative. Patients with severe COVID-19 and diabetes mellitus have the lowest lymphocyte counts compared with those with severe COVID-19 without Diabetes Mellitus, and those with non-severe COVID-19 with or without diabetes mellitus. Partially decreased lymphocyte subsets, age and diabetes mellitus were closely related to disease progression and prognosis [33], since diabetes mellitus could lead to dysfunctional cellular immunity [34].

In conclusion, we assessed the relationship between symptomatology, coexisting health conditions, clinical measures and health assistance, with mortality risk in severe COVID-19 patients. We observed that cough and kidney failure triplicate the mortality risk and both bilirubin levels and oncologic condition are shown as the most associated with the demise, increasing in four and ten times the risk, respectively. Other clinical characteristics such as fever, diabetes mellitus, breathing frequency, neutrophil-lymphocyte ratio, oxygen saturation and troponin levels, were also related to mortality risk of in-hospital death. The present study shows that some symptomatology, comorbidities and clinical measures could be the target of prevention tools to improve survival rates.

Author contribution

Manuel Lozano: Conceptualization, Writing- Original draft preparation; Adina Iftimi: Methodology, Conceptualization, Writing – review & editing; Alvaro Briz-Redon: Visualization, Investigation, Writing – review & editing. Juanjo Peiró: Software, Validation, Writing – review & editing; Lara Manyes: Validation, Writing – review & editing; María Otero: Data curation, Writing – review & editing; Mayte Ballester: Data curation, Writing – review & editing; Dolores de las Marinas: Data curation, Writing – review & editing; Juan Carlos Catalá: Data curation, Writing – review & editing; José de Andrés: Supervision, Writing – review & editing; Carolina Romero: Conceptualization, Supervision, Writing – review & editing.

Data availability

The data that support the findings of this study are available from CHGUV. Restrictions apply to the availability of these data, which were used under license for this study.

Funding sources

This study was supported by the Innovation, Universities, Science and Digital Society Council through the Valencia Innovation Agency (AVI); grant 851255 from the European Research Council under the European Union's Horizon 2020 research and innovation program; and from the Universitat de València.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement

The study was approved by the institutional review board, and the requirement for informed consent was waived.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imj.2022.04.002.

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