REUE | Original Article

Causes of death in patients with COVID-19: the HUBCOVID365 cohort findings

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OBJECTIVES. To describe the causes of death in patients with COVID-19, analyze risk factors, and explore whether predictors differed according to cause of death.

MATERIAL AND METHODS. Data for the study cohort was gathered retrospectively by the working group on emergency care for patients with COVID-19 (HUBCOVID365) between March 1 and April 30, 2020. The group studied predictors of death from different causes and calculated adjusted odds ratios (ORs). Differences between 4 causes of death were analyzed, and 1-year survival curves were constructed.

RESULTS. We included 1601 patients and identified 276 deaths (17.6%): 209 deaths (75.7%) were due to a single lung injury, 34 (12.3%) were due to sepsis, 24 (8.7%) to cardiovascular complications, and 9 (3.3%) to other events. The adjusted ORs (95% CIs) for predictors of mortality overall and death due to lung injury, respectively, were age, 1.09 (1.06-1.12) and 1.11 (1.07-1.15); dyspnea 2.75 (1.68-4.51) and 2.08 (1.18-3.66); systolic blood pressure less than 100 mmHg, 3.82 (1.77-8.23) and 3.27 (1.36-7.84); respiratory rate over 24 rpm, 1.72 (1.05-2.79) and 2.21 (1.27-3.84); resting oxygen saturation less than 92%, 2.54 (1.48-4.37) and 2.34 (1.28-4.28); and D-dimer level 1000 ng/mL or higher, 2.69 (1.55-4.69) and 2.12 (1.14-3.93). Mortality attributed to sepsis was associated with intensive care unit admission and invasive mechanical ventilation. The survival curve for lung injury was significantly different from the others.

CONCLUSION. Patients with COVID-19 died mainly because of lung injury. Sepsis was the second most frequent cause of death. We detected few differences in predictors of death from different causes. These findings suggest that protocols for general measures to prevent thrombotic and septic complications should be continued for all patients with severe COVID-19.

Keywords: COVID-19. Mortality. Pneumonia. Cardiovascular complications. Infection. Lung injury.

Estudio de las diferentes causas de mortalidad en pacientes con COVID-19. Cohorte HUBCOVID365

OBJETIVOS. Describir, en pacientes con COVID-19, las diferentes causas de mortalidad, analizar las variables predictoras y si existen diferencias entre ellos.

MATERIAL Y MÉTODO. Pacientes de la cohorte retrospectiva HUBCOVID365, diagnosticados de COVID-19 entre el 1 de marzo y el 30 de abril de 2020. Se investigaron las variables predictoras de las diferentes causas de mortalidad y se calcularon las *odds ratio* (OR) ajustadas. Se analizan las diferencias entre las cuatro categorías de mortalidad y se completó el análisis con curvas de supervivencia al año de seguimiento.

RESULTADOS. Se identificaron 1.601 pacientes, de los cuales fallecieron 276 (17,6%): 209 (75,7%) por lesión pulmonar única, 34 (12,3%) por sepsis, 24 (8,7%) por causa cardiovascular y 9 (3,3%) por otras causas. Las OR ajustadas de las variables predictoras de mortalidad total y lesión pulmonar única fueron: edad 1,09 (IC 95%: 1,06-1,12) y 1,11 (IC 95%: 1,07-1,15), disnea 2,75 (IC 95%: 1,68-4,51) y 2,08 (IC 95%: 1,18-3,66), presión arterial sistólica < 100 mmHg 3,82 (IC 95%: 1,77-8,23) y 3,27 (IC 95%: 1,36-7,84), frecuencia respiratoria > 24 rpm 1,72 (IC 95%: 1,05-2,79) y 2,21 (IC 95%: 1,27-3,84), saturación basal de O_2 < 92% 2,54 (IC 95%: 1,48-4,37) y 2,34 (IC 95%: 1,28-4,28) y D-dímero ≥ 1.000 ng/ml 2,69 (IC 95%: 1,55-4,69) y 2,12 (IC 95%: 1,14-3,93); respectivamente. La mortalidad por sepsis se asoció al ingreso en cuidados intensivos y a ventilación mecánica invasiva. Las curvas de supervivencia mostraron diferencias significativas en la mortalidad por lesión pulmonar única.

CONCLUSIÓN. Los pacientes con COVID-19 que fallecen presentan sobre todo mortalidad relacionada con la lesión pulmonar única, seguida de la asociada a sepsis. Existen pocas diferencias en las variables predictoras y comparaciones según la tipología de mortalidad. En base a ello, se deben seguir estableciendo protocolos generales de profilaxis trombótica y de complicaciones sépticas en todos los pacientes que presentan COVID-19 grave.

Palabras clave: COVID-19. Mortalidad. Neumonía. Cardiovascular. Infección. Lesión pulmonar.

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Introduction

COVID-19 infection is a global disease. More than 645 million people have been infected worldwide, with over 6.5 million deaths.[1] Since its onset, it has had a significant impact on healthcare organization at all levels of care.[2-7] Its clinical presentation ranges from asymptomatic or mildly symptomatic forms (fever, dry cough, asthenia, myalgia, diarrhea, headache, loss of smell or taste) to severe cases with bilateral pneumonia leading to acute respiratory distress syndrome (ARDS), often requiring intensive care unit (ICU) admission for invasive life support and showing high mortality. This has made COVID-19 one of the leading causes of death worldwide.[8] Moreover, coexisting clinical conditions, such as cardiovascular diseases or cancer, are frequent and make patients more vulnerable, with more severe presentations and higher mortality.[9] In addition, the infection itself may exacerbate chronic diseases and lead to unusual complications, particularly of cardiovascular origin.[10-14] For all these reasons, there is an initial difficulty in determining the causal relationship between infection and cause of death. This occurs because different scenarios can be considered when interpreting COVID-19–related deaths: isolated pulmonary injury, the development of cardiovascular or septic complications, or, in some cases, COVID-19 acting as an epiphenomenon.[15,16]

The objective of this study was to describe the different causes of mortality in patients with COVID-19 infection, identify predictive variables, and analyze whether differences exist among them.

Materials and methods

We conducted this study in the emergency department of *Hospital Universitario Bellvitge* (Barcelona, Spain), a tertiary referral and community reference center for 201,192 inhabitants of L'Hospitalet and El Prat de Llobregat, and a referral center for high-technology procedures for more than 2 million inhabitants in the Southern Metropolitan Area, Camp de Tarragona, and Terres de l'Ebre. All cases of acute COVID-19 presenting to the hospital emergency department between March 1st and April 30th, 2020, were included. A case was defined as any patient aged ≥ 18 years who presented with symptoms consistent with acute COVID-19 infection and had a positive reverse transcription polymerase chain reaction (RT-PCR) test obtained from a nasopharyngeal swab at the time of emergency admission. Only the first emergency consultation episode was included, defining the index case. The details and characteristics of these patients have been published previously.[17]

Study design and variable selection

We conducted a retrospective observational study with a 1-year follow-up (HUBCOVID365 cohort). Data were obtained through review of emergency, inpatient, and primary care medical records. Investigators associated with the project determined the final COVID-19 diagnosis and whether death was directly related to the infection or due to another cause.

A total of 37 variables were collected: demographic variables (2): age and sex; comorbidities (12): hypertension, diabetes mellitus, dyslipidemia, chronic heart failure, chronic ischemic heart disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, stroke, chronic liver disease, preexisting cognitive impairment, active neoplasia, and immunosuppressive therapy; disease course: days since symptom onset; symptoms at presentation (5): fever, cough, dyspnea, GI symptoms (diarrhea, nausea, vomiting), and anosmia or ageusia; clinical signs (5): temperature, systolic blood pressure, heart rate (HR), respiratory rate, and baseline oxygen saturation; laboratory findings (7): C-reactive protein, alanine aminotransferase, lactate dehydrogenase, leukocyte count, lymphocyte count, platelet count, and D-dimer; radiologic findings (2): pulmonary infiltrates and laterality (unilateral or bilateral); and support measures (5): noninvasive mechanical ventilation, high-flow nasal oxygen therapy, invasive mechanical ventilation (IMV), corticosteroid therapy, and ICU admission.

The primary outcome variable was mortality at the 1-year follow-up. All cases were reviewed by the same research team, and only deaths related to the index episode were included. The investigators defined four categories of mortality: 1) mortality due to acute pulmonary injury caused by the infection, without other potentially fatal causes; 2) cardiovascular mortality, including death from acute heart failure, acute coronary syndrome, pulmonary embolism, stroke, or acute arterial ischemia; 3) septic mortality, due to infectious complications; 4) mortality from other causes, excluding the above.

Statistical analysis

Qualitative variables were expressed as frequencies and percentages. Associations were analyzed using the chi-square test (or Fisher's exact test, as appropriate) and one-way ANOVA for comparisons among > 2 categories. Quantitative variables were expressed as mean ± standard deviation (SD) if normally distributed (verified by the Kolmogorov-Smirnov test), or as median and interquartile range (IQR) otherwise. Associations were analyzed using the Student t test or Mann–Whitney U test, depending on distribution. Continuous variables were dichotomized based on clinically meaningful cut-off values.

Mortality analysis involved 3 types of comparisons: 1) Investigation of predictors of total mortality and mortality due to isolated pulmonary injury at one-year follow-up; 2) Comparison of mortality from isolated pulmonary injury versus other COVID-19–associated causes; 3) Comparison among the 4 defined mortality categories (acute pulmonary, septic, cardiovascular, other causes). The strength of association between predictive variables and mortality was expressed as adjusted odds ratios (ORs) with 95% confidence intervals (CIs), using logistic regression analysis including variables showing statistically significant differences in univariate analysis. Survival differences were assessed using Kaplan–Meier survival curves, compared with the log-rank test. A P value ≤ .05 or a 95%CI for the OR that excluded 1 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics version 26.

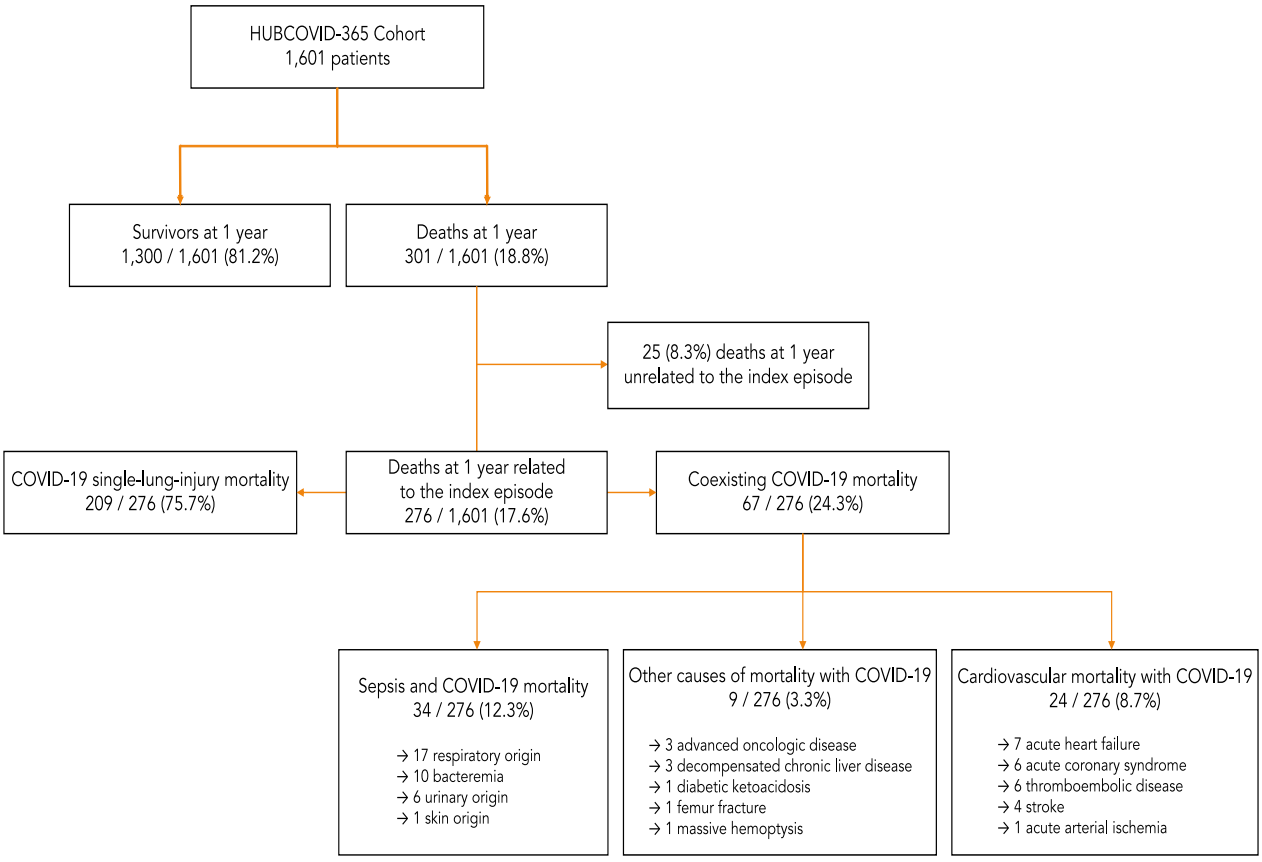

Figure 1. Flowchart of the HUBCOVID19 cohort.

Ethical considerations

The study was approved by *Hospital Universitario Bellvitge* Clinical Research Ethics Committee (reference PR182/20). Given the retrospective nature of the study, a waiver of written informed consent was granted. The research adhered to the ethical principles of the Declaration of Helsinki on human studies. Data were obtained from an anonymized database with coded patient identifiers to ensure confidentiality.

Results

A total of 1,601 patients presenting with acute, laboratory-confirmed COVID-19 infection at the time of admission were reviewed. As shown in Figure 1, a total of 276 patients died within one year in relation to the acute episode. Of these, 209 (75.7%) died from isolated pulmonary injury, 34 (12.3%) from sepsis, 24 (8.7%) from cardiovascular causes, and 9 (3.3%) from other causes. Table 1 describes the total study population. The mean age was 62.1 years (SD, 16.9), and 55.5% were men. The most frequent comorbidities were hypertension (45.9%) and dyslipidemia (37.2%). Most patients presented symptoms at arrival to the emergency department, abnormal laboratory findings (particularly elevated LDH and lymphopenia), and radiologic findings of pulmonary infiltrates, predominantly bilateral. Of the 39 variables studied, 33 were associated with total mortality and 34 with mortality due to isolated pulmonary injury (Table 1). However, in the adjusted multivariate analysis (Table 2), most variables lost statistical significance. For both total mortality and isolated pulmonary injury–related mortality, the predictive variables that remained significant in both groups were: age: OR 1.09 (95% CI, 1.06–1.12) and 1.11 (95% CI, 1.07–1.15); dyspnea: OR, 2.75 (95% CI, 1.68–4.51) and 2.08 (95% CI, 1.18–3.66); systolic blood pressure < 100 mm Hg: OR, 3.82 (95% CI, 1.77–8.23) and 3.27 (95% CI, 1.36–7.84); respiratory rate > 24 rpm: OR, 1.72 (95% CI, 1.05–2.79) and 2.21 (95% CI, 1.27–3.84); baseline O_2 saturation < 92%: OR, 2.54 (95% CI, 1.48–4.37) and 2.34 (95% CI, 1.28–4.28; and D-dimer ≥ 1,000 ng/mL: OR, 2.69 (95% CI, 1.55–4.69) and 2.12 (95% CI, 1.14–3.93), respectively. In the comparative analysis of the different types of mortality (Table 3), there were few differences between isolated pulmonary injury mortality and other causes. Patients who died from isolated pulmonary injury were older and had lower ICU admission and IMV rates. When analyzing the four mortality categories, the same significant differences were observed in age, ICU admission, and IMV use. In the survival analysis (Figure 2), significant differences were found: mortality due to isolated pulmonary injury occurred earlier than mortality from other causes.

Discussion

Our study analyzed the different causes of death in COVID-19 patients, most widely related to isolated pulmonary injury caused directly by SARS-CoV-2 infection. These results are consistent with autopsy findings, in which 70–

Table 1. Baseline characteristics, acute-episode variables, and predictors of overall mortality and COVID-19 single-lung-injury mortality from index episode to 1-year follow-up

	Total N = 1.601 n (%)	Missing values n (%)	Alive N = 1.325 n (%)	Total death N = 276 n (%)	Single-lung-injury death N = 209 n (%)	*P*-value†	*P*-value†
Demographics							
Age (years) [mean (SD)]	62.1 (16.9)	0 (0.0)	59.0 (16.4)	77.1 (7.7)	78.5 (8.3)	< .001	< .001
Male sex	889 (55.5)	0 (0.0)	697 (52.6)	192 (69.6)	146 (69.9)	< .001	< .001
Comorbidities							
Hypertension	726 (45.9)	19 (1.2)	534 (40.8)	192 (70.1)	151 (72.6)	< .001	< .001
Diabetes mellitus	343 (21.7)	20 (1.2)	242 (18.5)	101 (36.9)	81 (38.9)	< .001	< .001
Dyslipidemia	589 (37.2)	19 (1.2)	443 (33.9)	146 (53.3)	114 (54.8)	< .001	< .001
Chronic heart failure	106 (6.7)	19 (1.2)	62 (4.7)	44 (16.1)	35 (16.8)	< .001	< .001
Chronic ischemic heart disease	91 (5.8)	19 (1.2)	59 (4.5)	32 (11.7)	26 (12.5)	< .001	< .001
Chronic obstructive pulmonary disease	123 (7.8)	21 (1.3)	81 (6.2)	42 (15.4)	38 (18.4)	< .001	< .001
Chronic kidney disease	200 (12.6)	19 (1.2)	135 (10.3)	65 (23.7)	53 (25.5)	< .001	< .001
Stroke	98 (6.2)	20 (1.2)	60 (4.6)	38 (13.9)	27 (13.0)	< .001	< .001
Chronic liver disease	53 (3.4)	19 (1.2)	39 (3.0)	14 (5.1)	12 (5.8)	.075	.037
Prior cognitive impairment	107 (6.8)	19 (1.2)	56 (4.3)	51 (18.6)	43 (20.7)	< .001	< .001
Active neoplasm	140 (8.9)	20 (1.2)	93 (7.1)	47 (17.2)	38 (18.3)	< .001	< .001
Treatment with immunosuppressants	113 (7.1)	19 (1.2)	86 (6.6)	27 (9.9)	19 (9.1)	.055	.231
Symptoms at ED presentation							
Symptom onset (days) [mean (SD)]	7.4 (5.0)	31 (1.9)	7.7 (4.8)	6.3 (5.1)	6.2 (5.1)	< .001	< .001
Fever	1313 (83.0)	19 (1.2)	1104 (84.4)	209 (76.3)	162 (77.9)	.001	.035
Cough	1157 (73.2)	20 (1.2)	972 (74.3)	185 (67.8)	142 (68.6)	.026	.110
Dyspnea	693 (43.8)	20 (1.2)	526 (40.2)	167 (61.2)	127 (61.4)	< .001	< .001
Diarrhea, nausea, or vomiting	528 (33.4)	21 (1.3)	465 (35.6)	63 (23.1)	48 (23.2)	< .001	.001
Anosmia or ageusia	277 (17.6)	30 (1.9)	265 (20.3)	12 (4.5)	7 (3.5)	< .001	< .001
Signs at ED							
Temperature ≥ 38°C	279 (18.5)	96 (6.0)	223 (17.8)	56 (22.0)	43 (22.4)	.123	.141
SBP < 100 mmHg	90 (5.9)	69 (4.3)	62 (4.9)	28 (10.6)	22 (11.0)	< .001	.001
HR > 100 bpm	482 (31.3)	63 (3.9)	406 (31.9)	76 (28.7)	54 (27.0)	.305	.156
RR > 24 rpm	410 (26.9)	79 (4.9)	274 (21.8)	136 (51.7)	109 (54.8)	< .001	< .001
Baseline O_2 saturation < 92%	217 (13.9)	37 (2.3)	110 (8.5)	107 (39.1)	82 (39.4)	< .001	< .001
Laboratory findings							
CRP ≥ 55 mg/L	738 (48.4)	77 (4.8)	547 (43.6)	191 (71.0)	147 (72.4)	< .001	< .001
ALT ≥ 40 IU/L	386 (27.8)	213 (13.3)	341 (29.4)	45 (19.7)	31 (17.9)	.003	.002
LDH ≥ 250 IU/L	772 (65.5)	423 (26.4)	617 (62.3)	155 (82.4)	114 (82.6)	< .001	< .001
Leukocytes < 4,000/mm^3	205 (13.4)	69 (4.2)	177 (14.0)	28 (10.3)	18 (8.8)	.105	.038
Lymphocytes < 1,000/mm^3	788 (51.4)	69 (4.2)	592 (46.9)	196 (72.6)	148 (72.5)	< .001	< .001
Platelets < 150,000/mm^3	353 (23.1)	69 (4.2)	283 (22.4)	70 (26.0)	56 (27.6)	.206	.101
D-dimer ≥ 1,000 ng/mL	151 (11.4)	280 (17.5)	92 (8.4)	59 (26.0)	41 (24.0)	< .001	< .001
Radiological findings							
Pulmonary infiltrates	1361 (86.8)	33 (2.1)	1113 (85.9)	248 (91.2)	191 (92.7)	.019	.007
Bilateral involvement	1026 (75.8)	240 (2.1)	812 (73.4)	214 (86.6)	163 (85.8)	< .001	.001
Support requirements							
Need for NIV	84 (5.4)	34 (2.1)	37 (2.9)	47 (17.2)	37 (17.8)	< .001	< .001
Need for HFNC	115 (7.3)	33 (2.1)	64 (4.9)	51 (18.6)	36 (17.3)	< .001	< .001
Corticosteroids	315 (19.7)	6 (0.4)	221 (16.7)	94 (34.6)	62 (30.0)	< .001	< .001
ICU admission	103 (6.5)	7 (0.4)	54 (4.1)	49 (17.9)	20 (9.6)	< .001	.047
Need for IMV	99 (6.2)	7 (0.4)	47 (3.6)	52 (19.0)	24 (11.5)	< .001	.001

†*P*-value for the comparison between survivors and all deceased patients.
‡*P*-value for the comparison between survivors and deceased patients with single lung injury.
SD: standard deviation; SBP: systolic blood pressure; HR: heart rate; bpm: beats per minute; RR: respiratory rate; rpm: respirations per minute; CRP: C-reactive protein; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; NIV: non-invasive mechanical ventilation; HFNC: high-flow nasal cannula therapy; ICU: intensive care unit; IMV: invasive mechanical ventilation; ED: emergency department.

80% of cases show diffuse alveolar damage as the sole cause of death.[18] Severe forms of COVID-19 display a clinical profile similar to that reported in former studies, where older age, presence of comorbidities, elevated inflammatory markers, and lymphopenia are predictors of poor outcomes, helping identify patients with a worse prognosis.[19,20] Furthermore, these predictive variables appeared consistently in both total mortality and isolated pulmonary injury–related mortality. The proportion of COVID-19 patients who died from non-pulmonary causes was much smaller; however, they also exhibited a clinical severity profile similar to that of the first group.

Since the beginning of the pandemic, septic complications were identified as a major challenge, especially in ICU patients.[16,21] A systematic review reported a pooled prevalence of COVID-19 with bacterial coinfection of 24%

Table 2. Multivariate analysis of predictor variables for overall mortality and single–lung-injury mortality at 1-year follow-up from the index episode

Predictor variables	Overall mortality	Single-lung-injury mortality
	OR (95% CI); *P*-value†	OR (95% CI); *P*-value‡
Demographic data		
Age	1.09 (1.06-1.12); < .001	1.11 (1.07-1.15); < .001
Male sex	2.09 (1.24-3.53); .006	–
Comorbidities		
Stroke	–	0.33 (0.11-0.93); .036
Cognitive impairment	–	2.28 (1.04-4.97); .038
Episode signs and symptoms		
Dyspnea	2.75 (1.68-4.51); < .001	2.08 (1.18-3.66); .012
SBP < 100 mmHg	3.82 (1.77-8.23); .001	3.27 (1.36-7.84); .008
RR > 24 rpm	1.72 (1.05-2.79); .030	2.21 (1.27-3.84); .005
Baseline O_2 saturation < 92%	2.54 (1.48-4.37); .001	2.34 (1.28-4.28); .006
Laboratory findings		
Lymphocytes < 1,000/mm^3	1.97 (1.20-3.26); .008	–
D-dimer ≥ 1,000 ng/mL	2.69 (1.55-4.69); < .001	2.12 (1.14-3.93); .017

†Model adjusted for: age, male sex, hypertension, diabetes mellitus, dyslipidemia, chronic heart failure, chronic ischemic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, stroke, prior cognitive impairment, active neoplasia, days since symptom onset, fever, cough, dyspnea, diarrhea, nausea or vomiting, anosmia or ageusia, SBP < 100 mmHg, HR > 100 bpm, RR > 24 rpm, baseline O_2 saturation < 92%, CRP ≥ 55 mg/L, ALT ≥ 40 IU/L, LDH ≥ 250 IU/L, lymphocytes < 1,000/mm^3, D-dimer ≥ 1,000 ng/mL, presence of pulmonary infiltrates.
‡Model adjusted for: age, male sex, hypertension, diabetes mellitus, dyslipidemia, chronic heart failure, chronic ischemic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, stroke, chronic liver disease, prior cognitive impairment, active neoplasia, days since symptom onset, fever, dyspnea, diarrhea, nausea or vomiting, anosmia or ageusia, SBP < 100 mmHg, HR > 100 bpm, RR > 24 rpm, baseline O_2 saturation < 92%, CRP ≥ 55 mg/L, ALT ≥ 40 IU/L, LDH ≥ 250 IU/L, leukocytes < 4,000/mm^3, lymphocytes < 1,000/mm^3, D-dimer ≥ 1,000 ng/mL, presence of pulmonary infiltrates.
OR: odds ratio; CI: confidence interval; SBP: systolic blood pressure; RR: respiratory rate; rpm: respirations per minute.

(95%CI, 19–30), increasing to 41% (95% CI, 24–58) in ICU patients, and associated with increased mortality (OR, 3.31; 95% CI, 1.82–5.99).[22] In our study, the most prevalent septic complication was bacterial pneumonia, reflecting the greater need for ventilatory support therapies, such as high-flow nasal cannula oxygen and IMV. These complications usually resulted from invasive procedures required by critically ill patients, mostly those admitted to the ICU.[21,22] Unfortunately, we did not identify clinical characteristics at admission that could help predict which patients would develop these complications, probably because all patients were potential candidates for them—thus requiring general preventive protocols.

Another group of patients died from cardiovascular complications. SARS-CoV-2 induces a prothrombotic state through hypercoagulability, with a complex pathophysiology involving dysregulated interactions among the inflammatory, immune, coagulation, fibrinolytic, complement, kallikrein–kinin, and vascular endothelial systems, resulting in a procoagulant state.[23,24] This increases the risk of fatal thrombotic cardiovascular events, as observed in our study.[25-28] Most of these patients showed elevated plasma D-dimer, C-reactive protein, and fibrinogen levels.[28,29] In our cardiovascular mortality group, a higher proportion had D-dimer ≥ 1,000 ng/mL, though not significantly. They did not differ in cardiovascular risk factors or preexisting heart disease. Currently, clinicians must remain alert to the risk of thrombotic cardiovascular complications in SARS-CoV-2 infection, as these affect disease progression and prognosis.[30] Finally, a small group of patients had COVID-19 as an epiphenomenon, with death mainly related to underlying chronic conditions or acute non-COVID illnesses. These patients typically presented with fewer infection symptoms, lower inflammatory markers, and were identified incidentally through screening during hospitalization.

Our study has several limitations. The main one is its single-center design, which limits generalizability to other health care settings, as management protocols and complication detection may differ. Therapeutic limitation levels were not recorded, which could explain some mortality differences vs other centers. The study was conducted during the first wave, when knowledge of thrombotic complications and preventive treatments (eg, low-molecular-weight heparin) were limited, and specific therapies improving survival were not yet available. The population was unvaccinated. Nevertheless, our findings describe a situation that may still be relevant today, as vaccination and specific treatments have reduced acute pulmonary injury mortality, while septic and cardiovascular complications may now represent a larger proportion of COVID-19–related deaths.

Conclusions

Mortality in COVID-19 infection is primarily related to isolated pulmonary injury, although other clinical scenarios can cause death independent of direct viral lung injury. While predictive mortality variables are well established, differences by mortality type are minimal. Therefore, general preventive protocols for thrombotic and septic complications should continue to be applied to all patients with severe COVID-19, especially those requiring ICU admission.

Table 3. Comparative study of mortality categories from the acute episode to 1-year follow-up

	Single-lung-injury N = 209 n (%)	CV N = 24 n (%)	Sepsis N = 34 n (%)	Other causes N = 9 n (%)	*P*-value†	*P*-value‡
Demographics						
Age (years) [mean (SD)]	78.5 (8.3)	76.6 (13.1)	68.7 (11.0)	77.3 (9.9)	.001	< .001
Male sex	146 (69.9)	15 (62.5)	26 (76.5)	5 (55.6)	.625	.537
Comorbidities						
Hypertension	151 (72.6)	15 (65.2)	20 (58.8)	6 (66.7)	.105	.393
Diabetes mellitus	81 (38.9)	8 (34.8)	8 (23.5)	4 (44.4)	.205	.355
Dyslipidemia	114 (54.8)	14 (60.9)	13 (38.2)	5 (55.6)	.370	.280
Chronic heart failure	35 (16.8)	2 (8.7)	4 (11.8)	3 (33.3)	.538	.324
Chronic ischemic heart disease	26 (12.5)	1 (4.3)	3 (8.8)	2 (22.2)	.452	.462
Chronic obstructive pulmonary disease	38 (18.4)	1 (4.3)	1 (2.9)	2 (22.2)	.016	.048
Chronic kidney disease	53 (25.5)	4 (17.4)	5 (14.7)	3 (33.3)	.225	.415
Stroke	27 (13.0)	3 (13.0)	5 (14.7)	3 (33.3)	.450	.388
Chronic liver disease	12 (5.8)	1 (4.3)	0 (0.0)	1 (11.1)	.379	.438
Prior cognitive impairment	43 (20.7)	1 (4.3)	4 (11.8)	3 (33.3)	.120	.111
Active neoplasia	38 (18.3)	2 (8.7)	5 (14.7)	2 (22.2)	.384	.649
Treatment with immunosuppressants	19 (9.1)	1 (4.3)	4 (11.8)	3 (33.3)	.478	.085
Episode symptoms						
Symptom onset (days) [mean (SD)]	6.2 (5.1)	4.9 (4.2)	6.9 (3.7)	9.8 (9.4)	.636	.087
Fever	162 (77.9)	14 (60.9)	28 (82.4)	5 (55.6)	.267	.105
Cough	142 (68.6)	16 (69.6)	25 (73.5)	2 (22.2)	.602	.027
Dyspnea	127 (61.4)	16 (69.6)	20 (58.8)	4 (44.4)	.914	.610
Diarrhea, nausea, or vomiting	48 (23.2)	3 (13.0)	11 (32.4)	1 (11.1)	.938	.298
Anosmia or ageusia	7 (3.5)	2 (8.7)	3 (8.8)	0 (0.0)	.134	.339
Episode signs						
Temperature ≥ 38°C	43 (22.4)	2 (9.1)	11 (32.4)	0 (0.0)	.770	.100
SBP < 100 mmHg	22 (11.0)	2 (9.1)	2 (6.1)	2 (22.2)	.713	.555
HR > 100 bpm	54 (27.0)	6 (27.3)	14 (41.2)	2 (22.2)	.289	.380
RR > 24 rpm	109 (54.8)	8 (34.8)	15 (44.1)	4 (57.1)	.080	.235
Baseline O_2 saturation < 92%	82 (39.4)	8 (34.8)	14 (41.2)	3 (33.3)	.823	.945
Laboratory findings						
CRP ≥ 55 mg/L	147 (72.4)	13 (56.5)	25 (73.5)	6 (66.7)	.371	.436
ALT ≥ 40 IU/L	31 (17.9)	5 (26.3)	9 (29.0)	0 (0.0)	.246	.255
LDH ≥ 250 IU/L	114 (82.6)	13 (81.3)	24 (88.9)	4 (57.1)	.923	.274
Leukocytes < 4,000/mm^3	18 (8.8)	2 (8.7)	7 (20.6)	1 (11.1)	.139	.215
Lymphocytes < 1,000/mm^3	148 (72.5)	14 (60.9)	25 (73.5)	9 (100.0)	.977	.172
Platelets < 150,000/mm^3	56 (27.6)	4 (17.4)	7 (20.6)	3 (33.3)	.305	.589
D-dimer ≥ 1,000 ng/mL	41 (24.0)	7 (38.9)	9 (30.0)	2 (25.0)	.227	.537
Radiological findings						
Pulmonary infiltrates	191 (92.7)	20 (87.0)	30 (88.2)	7 (77.8)	.113	.322
Bilateral involvement	163 (85.8)	18 (90.0)	28 (93.3)	5 (71.4)	.473	.411
Support requirements						
Need for NIV	37 (17.8)	4 (17.4)	6 (17.6)	0 (0.0)	.621	.587
Need for HFNC	36 (17.3)	3 (13.0)	12 (35.3)	0 (0.0)	.324	.029
Corticosteroids	62 (30.0)	7 (31.8)	23 (67.6)	2 (22.2)	.004	< .001
ICU admission	20 (9.6)	8 (34.8)	20 (58.8)	1 (11.1)	< .001	< .001
Need for IMV	24 (11.5)	7 (30.4)	20 (58.8)	1 (11.1)	< .001	< .001

†Comparison between death due to single-lung injury and cardiovascular, septic, or other causes.
‡Comparison among the four mortality categories (one-way ANOVA).
CV: cardiovascular; SD: standard deviation; SBP: systolic blood pressure; HR: heart rate; bpm: beats per minute; RR: respiratory rate; rpm: respirations per minute; CRP: C-reactive protein; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; NIV: non-invasive mechanical ventilation; HFNC: high-flow nasal cannula therapy; ICU: intensive care unit; IMV: invasive mechanical ventilation.

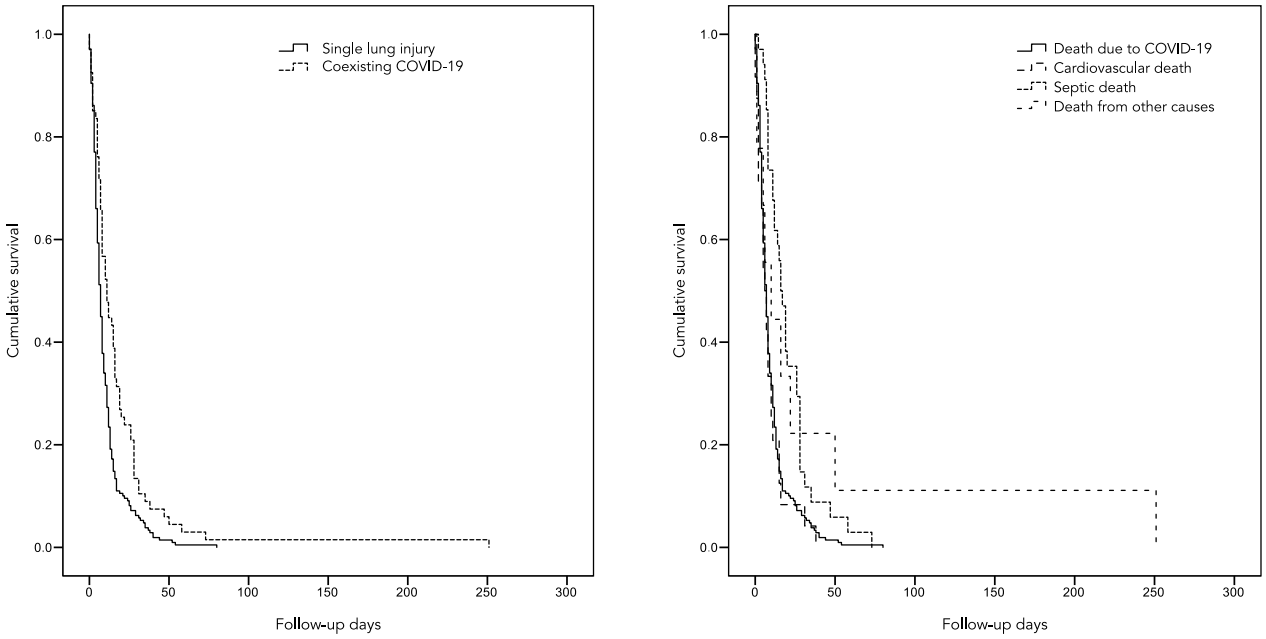

Figure 2. One-year survival curves for mortality related to the index episode.

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ADDENDUM

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REFERENCES

1. WHO Coronavirus Disease (COVID-19) Dashboard. (Accessed 14 Diciembre 2022).Available at: https://covid19.who.int/
2. Solà S, Jacob J, Azeli Y, Trenado J, Morales-Álvarez J, Jiménez-Fàbrega FX. Desarrollo y validación prospectiva de la escala TIHCOVID: una herramienta de triaje y priorización del traslado interhospitalario de pacientes COVID-19 graves. Emergencias. 2022;34:29-37.
3. Moreno-Pérez O, Ribes I, Fuertes-Kenneally L, Carratala JM, Román F, Otero-Rodríguez S, et al. Modelo asistencial ambulatorio de alta resolución COVID-A2R: una solución efectiva en el servicio de urgencias para pacientes con COVID-19 y riesgo de evolución desfavorable. Emergencias. 2022;34:103-10.
4. Albert A, Llorens P, Aguirre A, Martín-Sánchez FJ, Mínguez S, Moreno O, et al. Revisit after discharge from the emergency department in a cohort of patients with COVID-19 pneumonia and analysis based on the healthcare resource used for follow-up. RESALSEVID study. J Healthc Qual Res. 2022:S2603-6479(22)00050-1.
5. Navalpotro-Pascual JM, Fernández Pérez C, Peinado Vallejo A, Carrillo Alvarez A, Muñecas Cuesta Y, Muñoz Isabel B, et al. Actividad y asistencia a la parada cardiorrespiratoria en un servicio extrahospitalario de emergencias durante la pandemia COVID-19. Emergencias. 2021;33:100-6.
6. Estella A. Aprender de la pandemia: clave para combatir la saturación de los servicios de urgencias. Emergencias. 2022;34:141-3.
7. Alquézar-Arbé A, Miró Ò, Piñera P, Jacob J, Martín A, Agra Montava I, et al. Análisis de la evolución de consultas atendidas en los servicios de urgencias españoles durante la primera ola pandémica. An Sist Sanit Navar. 2021;44:243-52.
8. Czeisler MÉ, Marynak K, Clarke KEN, Salah Z, Shakya I, Thierry JM, et al. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1250-7.
9. Bigdelou B, Sepand MR, Najafikhoshnoo S, Negrete JAT, Sharaf M, Ho JQ, et al. COVID-19 and Preexisting Comorbidities: Risks, Synergies, and Clinical Outcomes. Front Immunol. 2022;13:890517.
10. Miró O, González Del Castillo J. Red de investigación SIESTA: memoria de resultados de su primer reto investigador (reto COVID-19). Emergencias. 2022;34:225-7.
11. García-Lamberechts EJ, Miró Ò, Fragiel M, Llorens P, Jiménez S, Piñera P, et al; Spanish Investigators on Emergency Situations TeAm (SIESTA) network. A case-control analysis of stroke in COVID-19 patients: Results of unusual manifestations of COVID-19-study 11. Acad Emerg Med. 2021;28:1236-50.
12. Mirò Ò, Sabaté M, Jiménez S, Mebazaa A, Martínez-Nadal G, Piñera P, et al; Spanish Investigators on Emergency Situations TeAm (SIESTA) network; SIESTA network. A case-control, multicentre study of consecutive patients with COVID-19 and acute (myo)pericarditis: incidence, risk factors, clinical characteristics and outcomes. Emerg Med J. 2022;39:402-10.
13. Miró Ò, Jiménez S, Mebazaa A, Freund Y, Burillo-Putze G, Martín A, et al; Spanish Investigators on Emergency Situations TeAm (SIESTA) network. Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. Eur Heart J. 2021;42:3127-42.
14. Alquézar-Arbé A, Miró Ò, Castillo JGD, Jiménez S, Llorens P, Martín A, et al; Spanish Investigators on Emergency Situations TeAm (SIESTA) Network. Incidence, Clinical Characteristics, Risk Factors and Outcomes of Acute Coronary Syndrome in Patients With COVID-19: Results of the UMC-19-S1010. J Emerg Med. 2022;62:443-54.
15. Degarege A, Naveed Z, Kabayundo J, Brett-Major D. Heterogeneity and Risk of Bias in Studies Examining Risk Factors for Severe Illness and Death in COVID-19: A Systematic Review and Meta-Analysis. Pathogens. 2022;11:563.
16. Vincent JL, Taccone FS. Understanding pathways to death in patients with COVID-19. Lancet Respir Med. 2020;8:430-2.
17. Albert A, Jacob J, Malchair P, Llopis F, Fuentes L, Martín C, et al. Predictores de revisita en pacientes con infección aguda COVID-19 con seguimiento al año: estudio de cohorte HUBCOVID365. Emergencias. 2022;34:38-46.
18. Romanova ES, Vasilyev VV, Startseva G, Karev V, Rybakova MG, Platonov PG. Cause of death based on systematic post-mortem studies in patients with positive SARS-CoV-2 tissue PCR during the COVID-19 pandemic. J Intern Med. 2021;290:655-65.
19. Fresco L, Osorio G, Carbó M, Marco DN, García-Gozalbes J, Artajona L, et al; Grupo

de Trabajo sobre la atención de la COVID-19 en Urgencias (COVID19-URG). Risk score for mortality due to COVID-19: a prospective temporal validation cohort study in the emergency department of a tertiary care hospital. Emergencias. 2022;34:196-203.
20. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. BMC Infect Dis. 2021;21:855.
21. Giannitsioti E, Louka C, Mamali V, Kousouli E, Velentza L, Papadouli V, et al. Bloodstream Infections in a COVID-19 Non-ICU Department: Microbial Epidemiology, Resistance Profiles and Comparative Analysis of Risk Factors and Patients' Outcome. Microorganisms. 2022;10:1314.
22. Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. PLoS One. 2021;16:e0251170.
23. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost. 2020;18:1559-1561.
24. Conway EM, Mackman N, Warren RQ, Wolberg AS, Mosnier LO, Campbell RA, et al. Understanding COVID-19-associated coagulopathy. Nat Rev Immunol. 2022;5:1-11.
25. Sagris D, Papanikolaou A, Kvernland A, Korompoki E, Frontera JA, Troxel AB, et al. COVID-19 and ischemic stroke. Eur J Neurol. 2021;28:3826-36.
26. Poor HD. Pulmonary Thrombosis and Thromboembolism in COVID-19. Chest. 2021;160:1471-80.
27. Zhao YH, Zhao L, Yang XC, Wang P. Cardiovascular complications of SARS-CoV-2 infection (COVID-19): a systematic review and meta-analysis. Rev Cardiovasc Med. 2021;22:159-65.
28. Pellegrini D, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, et al. Microthrombi as a Major Cause of Cardiac Injury in COVID-19: A Pathologic Study. Circulation. 2021;143:1031-42.
29. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844-7.
30. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, et al.; Asian Critical Care Clinical Trials Group. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med. 2020;8:506-517. Erratum in: Lancet Respir Med. 2020;8:e42.