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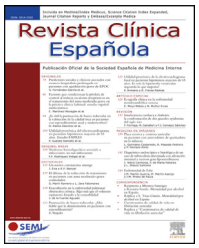

ORIGINAL ARTICLE

Impact of days elapsed from the onset of symptoms to hospitalization in COVID-19 in-hospital mortality: Time matters

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KEYWORDS
Prognostic factors;
COVID-19;
SARS-CoV-2

Abstract
Background: COVID-19 shows different clinical and pathophysiological stages over time. The effect of days elapsed from the onset of symptoms (DEOS) to hospitalization on COVID-19 prognostic factors remains uncertain. We analyzed the impact on mortality of DEOS to hospitalization and how other independent prognostic factors perform when taking this time elapsed into account.
Methods: This retrospective, nationwide cohort study, included patients with confirmed COVID-19 from February 20th and May 6th, 2020. The data was collected in a standardized online data capture registry. Univariate and multivariate COX-regression were performed in the general cohort and the final multivariate model was subjected to a sensitivity analysis in an early presenting (EP; <5 DEOS) and late presenting (LP; ≥5 DEOS) group.
Results: 7915 COVID-19 patients were included in the analysis, 2324 in the EP and 5591 in the LP group. DEOS to hospitalization was an independent prognostic factor of in-hospital mortality in the multivariate Cox regression model along with other 9 variables. Each DEOS increment accounted for a 4.3% mortality risk reduction (HR 0.957; 95% CI 0.93–0.98). Regarding variations in other mortality predictors in the sensitivity analysis, the Charlson Comorbidity Index only remained significant in the EP group while D-dimer only remained significant in the LP group.
Conclusion: When caring for COVID-19 patients, DEOS to hospitalization should be considered as their need for early hospitalization confers a higher risk of mortality. Different prognostic factors vary over time and should be studied within a fixed timeframe of the disease.
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PALABRAS CLAVE
Factores pronósticos;
COVID-19;
SARS-CoV-2

Impacto de los días transcurridos desde el inicio de los síntomas hasta la hospitalización en la mortalidad hospitalaria por COVID-19: el tiempo importa

Resumen
Introducción: El impacto de los días transcurridos desde el inicio de los síntomas (DTIS) hasta la hospitalización en los factores pronósticos de COVID-19 es incierto. Hemos analizado el efecto de los DTIS sobre la mortalidad intrahospitalaria y cómo se comportan otros factores pronósticos en función de los DTIS al ingreso.
Métodos: Estudio retrospectivo, multicéntrico y nacional (SEMI-COVID), con pacientes hospitalizados por COVID-19 entre el 20 de febrero de 2020 y el 6 de mayo de 2020. Se realizó una regresión COX univariante y multivariante en la cohorte general y el modelo final se sometió a un análisis de sensibilidad en un grupo de presentación precoz (<5 DTIS) y presentación tardía (≥5 DTIS).
Resultados: Se analizaron 7.915 pacientes con COVID-19, 2.324 en el grupo precoz y 5.591 en el tardío. Los DTIS hasta la hospitalización fueron un factor pronóstico independiente de mortalidad junto con otras 9 variables. Cada incremento de DTIS representó una reducción del riesgo de mortalidad del 4,3% (HR 0,957; IC del 95%: 0,93–0,98). En el análisis de sensibilidad, el índice de comorbilidad de Charlson sólo se mantuvo significativo en el grupo precoz mientras que el dímero D solo se mantuvo significativo en el grupo tardío.
Conclusión: Los DTIS al ingreso deben tenerse en cuenta cuando se atiende a pacientes con COVID-19, ya que la necesidad de una hospitalización temprana confiere un mayor riesgo de mortalidad. Otros factores pronósticos varían a lo largo del curso de la COVID-19 y deberían ser estudiados en franjas temporales concretas de la enfermedad.
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Introduction

Q5 The COVID-19 pandemic spread throughout the world at an unprecedented speed after the first cases of SARS-CoV-2-related disease were reported in Wuhan (China) in December 2019. Spain has been severely affected by the pandemic, with 12,549,053 COVID-19 cases, making it the fourth most affected country in Europe[1]. Early along in the epidemics, Siddiqi et al. proposed a sequential pathological process for COVID-19[2]. An initial viral phase with upper respiratory and lung injury-driven pneumonia[3,4] is, in some patients, later followed by an inadequate immune response driven by hyperinflammation and immunosuppression of varying degrees of severity[5]. In fact, macrophage activation and a

''cytokine storm'' have both been proposed as the basis for the acute respiratory distress syndrome (ARDS) seen in severe COVID-19[6,7]. Other lung injury mechanisms, such as endothelialitis and microvascular thrombosis, have also been found to be relevant in autopsy findings, which may evolve during hospitalization[8].

Several clinical, laboratory, and radiographic characteristics have been identified as independent risk factors for critical illness or death[9,10]. A temporal relationship has also been observed between days elapsed from the onset of symptoms (DEOS) and relevant clinical events such ARDS and intensive care unit admission[11,12]. Despite these findings, previous multicenter studies with large cohorts of patients have not addressed the relationship between DEOS to hospital admission and COVID-19 mortality and it has not been included on the prognostic models in order to fit them in the context of a timeframe[13,14].

DEOS is patient-subjective, but it is an easily ascertained variable for identifying different subgroups of patients in different stages of the disease. Previous studies have not sufficiently stressed the relevance of the number of DEOS to hospital admission related to other prognostic factors of the disease. The main objective of our study is to explore the impact of DEOS to hospitalization on COVID-19 related in-hospital death and how independent prognostic factors of in-hospital death perform within a stratified prediction model after dividing our cohort into early- and late-presenting groups according to DEOS.

Methods

Study design and participants

The SEMI-COVID-19 Registry is an ongoing, multicenter, nationwide, retrospective, observational study that includes data on adult patients admitted to Spanish hospitals with confirmed COVID-19[15]. The first admission included in this registry was on February 20, 2020. This study includes all eligible patients hospitalized from that date to May 6, 2020. The largest number of new SARS-CoV-2 infections recorded in Spain during the first wave of the pandemic was on March 25, 2020[16].

The SEMI-COVID-19 Registry was created during the pandemic with the objective of recording detailed clinical information on COVID-19 patients. It is coordinated by the Spanish Society of Internal Medicine and more than one hundred Spanish hospitals participate in it. The registry inclusion criteria are age $\geq$18 years and hospital admission for confirmed COVID-19[17]. For our analysis we included patients who were admitted during the first 15 days from symptoms onset, were able to self-report the date of symptoms onset (did not have dementia nor had a severely dependent baseline status defined as a Barthel Index $\leq$60[18,19]), were admitted for > 24 h and who were infected with SARS-CoV-2 outside of the hospital (onset of COVID-19 symptoms before hospital admission or $\leq$7 days after it).

The registry was first approved by the Provincial Research Ethics Committee of Málaga (Spain), and was subsequently approved by each participating hospital's research ethics committee. Written informed consent was obtained from all patients before inclusion in the registry and when this was not possible informed consent was requested verbally and recorded on the patient's medical chart.

Data collection

All data was extracted from electronic medical records by trained physicians by using a standardized online data capture system. A database manager verified the consistency of the recorded data. Demographic information and comorbidities (according to the International Statistical Classification of Diseases and Related Health Problems—10th revision[20]) were collected for analysis. Relevant treatments during hospitalization were also registered. Laboratory confirmation of SARS-CoV-2 infection was required for every patient and was done so via a reverse transcription polymerase chain reaction (RT-PCR) test of respiratory samples—mainly nasopharyngeal or oropharyngeal swabs and sputum—according to local hospital procedures. Patients were managed according to local criteria, although national recommendations provided by the Ministry of Health guided the clinical management, treatment, and discharge criteria[21].

Data from routine blood examinations upon admission included a complete blood count, coagulation profile, and serum biochemical tests (electrolytes, renal and liver function parameters, lactate dehydrogenase, myocardial enzymes, C-reactive protein, IL-6, and serum ferritin). Chest X-rays were available for all patients. The frequency of subsequent additional tests was determined by the attending physician.

Definitions and outcomes

The primary endpoint was in-hospital mortality, defined as death due to any cause during hospitalization. In order to explore the influence of COVID-19 timeframes on the impact of predictors of in-hospital mortality, the cohort was divided into an early-presenting group (EP) and a late-presenting (LP) group, depending on whether DEOS to hospital admission was less than 5 days or greater to or equal than 5 days, respectively. This cut-off point was defined according to the early viral disease period defined for the use of antiviral medications in clinical trials[22,23].

ARDS was diagnosed according to the Berlin Definition[24]. It was identified either by means of the oxygen saturation (SpO_2; measured with finger pulse oximetry) to fraction of inspired oxygen (FiO_2) ratio or the partial pressure of oxygen (PaO2) to FiO_2 ratio through the established correlation of the two measures: SpO_2/FiO_2 ratios of 235 and 315 correlate to PaO_2/FiO_2 ratios of 200 and 300, respectively[25]. Organ failure at admission was evaluated using the quick Sequential Organ Failure Assessment (qSOFA)[26]. Comorbidity was evaluated via the Charlson Comorbidity Index[27]. End-organ cardiovascular disease was defined as the presence of coronary heart disease, stroke, transient ischemic attack, or peripheral artery disease, according to World Health Organization's definition of cardiovascular diseases[28]. Renal function was estimated using the CKD-EPI equation[29]. Neutrophil-to-lymphocyte ratio was calculated because it has been shown to independently predict critical illness in COVID-19 patients[9].

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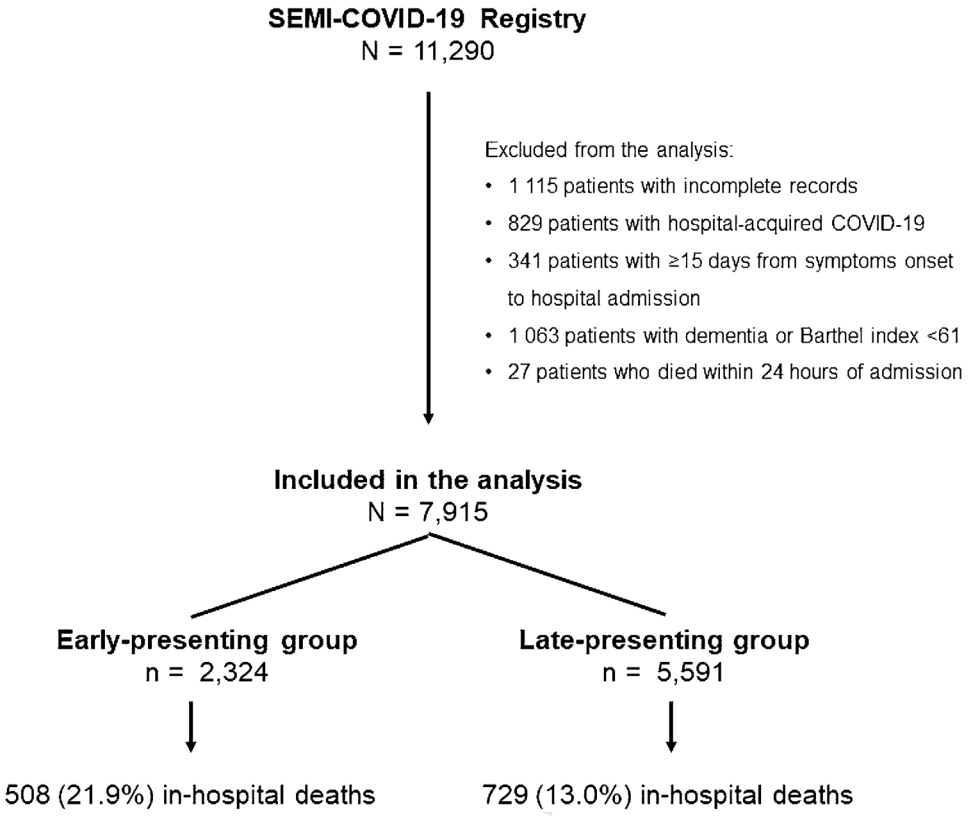

Figure 1 Patient inclusion flowchart.

Statistical analysis

Quantitative variables are shown as mean ± standard deviation (SD) or median and interquartile range (IQR). Qualitative variables are expressed as absolute and relative frequencies with percentages. Prognostic factors of in-hospital mortality were analyzed using univariate and multivariate Cox regression models. The variables that were finally included in the multivariate Cox regression model were prioritized using a random forest selection method and according to clinical criteria, previously published manuscripts, and availability of data (some variables, such as IL-6, had a high percentage of missing values). The multivariate Cox regression model was then stratified according to the prespecified early- and late-presenting groups. Statistical analyses and graphs were done using the R Software (v3.6.2) and Prism GraphPad (v7.00).

Results

Participants

A total of 11,290 patients had been included in the SEMI-COVID-19 Registry as of May 21, 2020. Of them, 7915 patients were included in this study (Fig. 1). All patients analyzed had met a hard endpoint at the time of analysis: they were either discharged home or had died. In our study population, 1237 patients died during hospitalization and 6678 were discharged.

The median age was 66.6 years (IQR 54.1–76.6) with 2326 patients (29.4%) who were 75 years of age or older. Most patients were male (4663; 58.9%) and Caucasian (6836; 87.9%). The median time from symptoms onset to hospital admission was 7 days (IQR 4–9). Almost half of the cohort had a Charlson Comorbidity Index ≥1 (3598; 47.0%) and cardiovascular comorbidities such as hypertension (3756; 47.6%), diabetes (1370; 17.4%), and end-organ cardiovascular disease (1087; 13.8%) were the most prevalent of them. Other relevant diseases were chronic obstructive pulmonary disease (542; 6.9%), chronic kidney disease (389; 5.0%), and chronic liver disease (28; 3.6%). The most common immunosuppressive states were malignancy (738; 9.4%) and chronic corticosteroid use (336; 4.3%). Other baseline characteristics are listed in Table 1.

Upon admission, mild ARDS (SpO_2/FiO_2 ratio < 315 and ≥ 235) was present in 686 patients (9.1%) and lung infiltrates were present in 6996 (89.1%). Other findings at hospital admission are shown in Table 2. During hospitalization, 1817 (23.1%) patients developed moderate or severe ARDS and 732 (9.3%) were admitted to the intensive care unit. In terms of treatment, most patients received lopinavir/ritonavir (LPVr; 5371; 68.4%), hydroxychloroquine (7019; 89.2%), or systemic corticosteroids (2684; 34.3%) either alone or in combination (Appendix Table 1 in Supplementary materials). The median length of hospital stay was 9 days (IQR 6–14).

Analysis of the early-presenting group versus the late-presenting group

The cohort was divided into EP and LP groups, with 2324 and 5591 patients each and 508 (21.9%) and 729 (13.0%) in-hospital deaths, respectively ($p < .001$). We found several

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Q1 **Table 1** Baseline characteristics of patients hospitalized with COVID-19.

	Total (N = 7915)	Early-presenting (n = 2324)	Late-presenting (n = 5591)	*p*
Days elapsed from the onset of symptoms to admission, median (IQR)	7 (4–9)	3 (2–4)	7 (6–10)	<.001
No. available	7915	2324	5591	
Age, median (IQR)	66.6 (54.1–76.6)	71.7 (57.6–80.8)	64.7 (53.1–74.9)	<.001
No. available	7915	2324	5591	
≥65 years, no./total no. (%)	4223/7915 (53.4)	1469/2324 (63.2)	2754/5591 (49.3)	<.001
≥80 years, no./total no. (%)	1383/7915 (17.5)	632/2324 (27.2)	751/5591 (13.4)	<.001
Male sex no./total no. (%)	4663/7915 (58.9)	982/2324 (42.3)	2270/5591 (40.6)	.173
Weight				
BMI, median (IQR)	27.8 (25.3–31.4)	27.8 (25.0–31.5)	27.8 (25.4–31.4)	.398
No. available	3598	1056	2542	
Obesity (BMI ≥ 30)	1239/3598 (34.4)	362/1056 (34.3)	877/2542 (34.5)	.899
Current smoker, no./total no. (%)	417/7541 (5.5)	163/2207 (7.4)	254/5334 (4.8)	<.001
Race, no./total no. (%)				
Caucasian	6836/7778 (87.9)	2025/2287 (88.5)	4811/5491 (87.6)	.253
Hispanic	774/7778 (10.0)	209/2287 (9.1)	565/5491 (10.3)	.122
Charlson Comorbidity Index, median (IQR)	0 (0–1)	1 (0–2)	0 (0–1)	<.001
No. available	7658	2235	5423	
Charlson Comorbidity Index ≥ 1, no./total no. (%)	3598/7658 (47.0)	1284/2235 (57.4)	2314/5423 (42.7)	<.001
Age-adjusted Charlson Comorbidity Index, median (IQR);	3 (1–4)	4 (2–5)	3 (1–4)	<.001
No. available	7658	2235	5423	
≥1 points, no./total no. (%)	6562/7658 (85.7)	1979/2235 (88.5)	4583/5423 (84.5)	.047
≥4 points, no./total no. (%)	2975/7658 (38.8)	1181/2235 (52.8)	1794/5423 (33.1)	<.001
Functional status moderately dependent, no./total no. (%)	464/7797 (6.0)	256/2278 (11.2)	208/5519 (3.8)	<.001
Cardiovascular comorbidities, no./total no. (%)				
Hypertension	3756/7896 (47.6)	1271/2317 (54.9)	2485/5579 (44.5)	<.001
Coronary artery disease[1]	590/7899 (7.5)	223/2317 (9.6)	367/5582 (6.6)	.033
Previous stroke or transient ischemic attack (TIA)	369/7877 (4.7)	147/2315 (6.3)	222/5562 (4.0)	<.001
Peripheral artery disease (PAD)	306/7887 (3.9)	118/2312 (5.1)	188/5575 (3.4)	<.001
End-organ cardiovascular disease (coronary heart disease, stroke or TIA, or PAD)	1087/7860 (13.8)	410/2309 (17.8)	677/5551 (12.2)	<.001
Congestive heart failure	437/7896 (5.5)	208/2316 (9.0)	229/5580 (4.1)	<.001
Atrial fibrillation	690/7889 (8.7)	284/2315 (12.3)	406/5574 (7.3)	<.001
Diabetes mellitus[2], no./total no. (%)	1370/7883 (17.4)	521/2314 (22.5)	849/5569 (15.2)	.004
Presence of diabetes-related complications[3]	359/7887 (4.6)	148/2316 (6.4)	211/5571 (3.8)	<.001
Patients receiving insulin	387/7722 (5.0)	155/2258 (6.9)	232/5464 (4.2)	<.001
Chronic respiratory disease, no./total no. (%)				
Chronic obstructive pulmonary disease (COPD)	542/7895 (6.9)	245/2314 (10.6)	297/5581 (5.3)	<.001
Asthma	652/7891 (8.3)	182/2314 (7.9)	470/5577 (8.4)	.409
Obstructive sleep apnea	529/7849 (6.7)	176/2297 (7.7)	353/5552 (6.4)	.036
Chronic kidney disease, no./total no. (%)	389/7840 (5.0)	180/2295 (7.8)	209/5545 (3.8)	<.001
Advanced chronic kidney disease[4]	378/7890 (4.8)	178/2312 (7.7)	200/5578 (3.6)	<.001
Patient on dialysis	69/7857 (0.9)	38/2302 (1.7)	31/5555 (0.6)	<.001
Chronic liver disease (any stage)[5], no./total no. (%)	287/7876 (3.6)	95/2311 (4.1)	192/5565 (3.5)	.154
Advanced chronic liver disease[6]	75/7893 (1.0)	28/2317 (1.2)	47/5576 (0.8)	.127
Malignancy, no./total no. (%)	738/7871 (9.4)	303/2311 (13.1)	435/5560 (7.8)	<.001
Solid tumor[7]	599/7885 (7.6)	253/2312 (10.9)	346/5573 (6.2)	<.001
Metastatic solid tumor	149/7890 (1.9)	67/2314 (2.9)	82/5576 (1.5)	<.001
Blood cancer[8]	160/7887 (2.0)	59/2316 (2.5)	101/5571 (1.8)	.035
Immunosuppression, no./total no. (%)				
HIV infection	63/7863 (0.8)	23/2307 (1.0)	40/5556 (0.7)	.210
Systemic rheumatic diseases[9]	179/7884 (2.3)	63/2308 (2.7)	116/5576 (2.1)	.078

Table 1 (*Continued*)

	Total (N = 7915)	Early-presenting (n = 2324)	Late-presenting (n = 5591)	*p*
Solid organ transplantation	94/7741 (1.2)	32/2266 (1.4)	62/5475 (1.1)	.307
Chronic glucocorticoid use	336/7896 (4.3)	146/2317 (6.3)	190/5579 (3.4)	<.001
Previous chronic treatments, no./total no. (%)				
Anticoagulants[10]	733/7850 (9.3)	316/2301 (13.7)	417/5549 (7.5)	<.001
Low dose aspirin	1064/7836 (13.6)	385/2299 (16.7)	679/5537 (12.3)	<.001
Statins	2516/7838 (32.1)	818/2300 (35.6)	1698/5538 (30.7)	<.001
ACE inhibitor	1280/7842 (16.3)	428/2299 (18.6)	852/5543 (15.4)	<.001
ARB	1557/7844 (19.8)	508/2300 (22.1)	1049/5544 (18.9)	.001

ACE = Angiotensin-converting enzyme; ARB = Angiotensin II receptor blocker; BMI = Body mass index, calculated as the ratio of weight (kg)/height^2 (m); HIV = Human immunodeficiency virus.

[1] Previous myocardial infarction (either with enzyme elevation or ECG evidence of previous myocardial infarction) or history of angina pectoris.

[2] Diagnosis of diabetes mellitus that requires pharmacological therapy.

[3] Includes microvascular (retinopathy, nephropathy, and neuropathy), macrovascular (atherosclerosis), and peripheral neuropathic complications.

[4] Chronic kidney disease recorded in the medical chart and baseline serum creatinine $\geq$ 3 mg/dL.

[5] Includes any kind of chronic liver disease without evidence of portal hypertension.

[6] Includes any kind of chronic liver disease with evidence of portal hypertension: radiographic signs, portal territory varices, ascites, or hepatic encephalopathy.

[7] Includes any history of solid organ neoplasm that requires or has required treatment (surgery, chemotherapy, and/or radiotherapy) and is not considered to be cured (the patient requires specific oncology consultation for active treatment or monitoring).

[8] Includes leukemia, lymphoma, and myeloma and is not considered to be cured (requires specific hemato-oncology consultation for active treatment or monitoring).

[9] Includes: rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, mixed connective tissue disease, giant cell arteritis, and polymyalgia rheumatica.

[10] Oral anticoagulants or low-molecular-weight heparin.

significant differences at admission and during hospitalization between the two groups (Tables 1 and 2). Of note, EP patients were older than LP patients (71.7 vs 64.7 years; $p < .001$), had a higher percentage of comorbidities (Charlson Comorbidity Index, CCI, $\geq$1 57.4% vs 42.7%; $p < .001$), and were more commonly immunosuppressed either because of malignancy (13.1% vs 7.8%; $p < .001$) or chronic corticosteroid use (6.3% vs 3.4%; $p < .001$). At hospital admission, the EP patients had a lower level of systemic inflammation (Fig. 2) as shown by lower levels of CRP (4.6 vs 6.2 mg/dL; $p < .001$), ferritin (493 vs 694 ng/mL; $p < .001$), and fibrinogen (587 vs 637 mg/dL; $p < .001$). Upon arrival at the hospital, they also had a higher prevalence of mild ARDS (SpO_2/FiO_2 ratio < 315 and $\geq$ 235; 10.4% vs 8.5%; $p < .001$) and qSOFA $\geq$ 2 (6.9% vs 5.1%; $p < .001$) in spite of a lower frequency of lung infiltrates (82.7% vs 91.7%; $p < .001$). With respect to biochemical parameters, D-dimer levels were higher (620 vs 577 ng/mL; $p = .001$) and LDH was lower (289 vs 320 U/L; $p < .001$) in the EP group. The distribution over time of other clinical and biochemical data upon admission according to DEOS to hospital admission can be seen in Appendix Fig. 1 in Supplementary materials. Treatments received were similar except for LPVr (62.3% vs 70.9%; $p < .001$), hydroxychloroquine, (84.8% vs 91.0%; $p < .001$), and tocilizumab (8.9% vs 10.7%; $p < .001$), all of which were more frequently prescribed in the LP group (Appendix Table 1 in Supplementary materials). Moderate or severe ARDS was more frequently observed in the EP group (26.5% vs 21.7%; $p < .001$) and their median hospital stay was longer (9 days, IQR 6–15 vs 9 days, IQR 6–13; $p < .001$), but there were similar rates of intensive care unit admission (Appendix Table 2 in Supplementary materials).

Univariate and multivariate prediction models of in-hospital mortality in the cohort and sensitivity analysis of the multivariate model in early- and late-presenting groups

Several variables upon admission were shown to be statistically significant predictors of in-hospital mortality on the univariate Cox regression model of the entire cohort (Appendix Table 3 in Supplementary materials). They were prioritized for further analysis using the random forest selection method (Appendix Fig. 2 in Supplementary materials), significance on the univariate model, and clinical criteria based on previously published studies. In the end, 14 variables were analyzed on the multivariate Cox regression model. DEOS was determined to be an independent protective factor of in-hospital death (HR 0.962; 95% CI 0.938–0.986). Thus, each day elapsed accounted for a 4,3% mortality risk reduction. Another eight variables (age, SpO_2/FiO_2 ratio, CCI, CRP, D-dimer, LDH, estimated glomerular filtration rate, platelets and hemoglobin) were independent prognostic factors of in-hospital death (Fig. 3).

We performed a sensitivity analysis of the final multivariate Cox regression model in the EP and LP groups to gain further insight into how these prognostic factors changed over the course of the disease. In the LP the Charlson Comorbidity Index lost significance while in the EP group it

Table 2 Symptoms, vital signs, and laboratory tests at admission.

	Total (N = 7915)	Early-presenting (n = 2324)	Late-presenting (n = 5591)	*p*
Symptoms and signs, no./total no. (%)				
Dyspnea	4488/7873 (57.0)	1226/2313 (53.0)	3262/5560 (58.7)	<.001
Cough	9184/7891 (78.4)	1586/2315 (68.5)	4598/182.5 (82.5)	<.001
Productive cough	1282/6184 (20.7)	384/1586 (24.2)	898/4598 (19.5)	<.001
Anosmia or dysgeusia	665/7622 (8.7)	96/2231 (4.3)	569/5391 (10.6)	<.001
Arthralgia or myalgia	2686/7795 (34.5)	583/2283 (25.5)	2103/5512 (38.2)	<.001
Headache	1014/7772 (13.0)	218/2280 (9.6)	796/5492 (14.5)	<.001
Abdominal pain	548/7815 (7.0)	154/2286 (6.7)	394/5529 (7.1)	.540
Diarrhea	1949/7837 (24.9)	397/2297 (17.3)	1552/5540 (28.0)	<.001
Lung auscultation				
Crackles	4139/7724 (53.6)	1095/2252 (48.6)	3044/5472 (55.6)	<.001
Wheezing	455/7719 (5.9)	149/2248 (6.6)	306/5471 (5.6)	.079
Vital signs (no./total no. (%) or median (IQR))				
Temperature on admission, median (IQR)	37.0 (36.4–37.8)	37.0 (36.4–37.8)	37.0 (36.4–37.8)	.578
No. available	7610	2218	5392	
$\geq$38.0 °C	1680/7610 (22.1)	487/2218 (22.0)	1193/5392 (22.1)	.872
Systolic blood pressure, median (IQR)	128 (115–140)	130 (115–144)	127 (115–140)	<.001
No. available	7519	2213	5306	
Heart rate, median (IQR)	88 (77–100)	86 (76–99)	88 (78–100)	<.001
No. available	7619	2231	5388	
Altered mental status	490/7815 (6.3)	251/2289 (11.0)	239/5526 (4.3)	<.001
Respiratory rate $\geq$ 20 breaths/min	2260/7694 (29.4)	617/2266 (27.2)	1643/5428 (30.3)	.008
SpO_2/FiO_2, median (IQR)	465 (435–480)	470 (430–480)	465 (440–480)	.680
	7551	2201		
$SpO_2/FiO_2 \geq 315$	6865/7551 (90.9)	1971/2201 (89.6)	4894/5350 (91.5)	.008
$SpO_2/FiO_2 < 315$	686/7551 (9.1)	230/2201 (10.4)	456/5350 (8.5)	.008
$SpO_2/FiO_2 < 235$	267/7551 (3.5)	96/2201 (4.4)	3.2/5350 (3.2)	.013
qSOFA $\geq$ 2	411/7327 (5.6)	150/2169 (6.9)	261/5158 (5.1)	.002
Admission studies (no./total no. (%) or median (IQR))				
Complete blood count, median (IQR)				
Leukocyte count, $\times 10^9$/L	6.1 (4.7–8.1)	6.2 (4.60–8.4)	6.1 (4.7–7.9)	.050
No. available	7880	2309	5571	
Lymphocyte count, $\times 10^9$/L	0.94 (0.70–1.30)	0.91 (0.66–1.30)	0.95 (0.70–1.30)	.086
No. available	7856	2298	5558	
Lymphocytes, $<1000 \times 10^6$/L	4106/7856 (52.3)	1227/2298 (53.4)	2879/5558 (51.8)	.198
Neutrophil count, $\times 10^9$/L	4.38 (3.10–6.24)	4.40 (3.02–6.56)	4.35 (3.14–6.13)	.353
No. available	7828	2295	5533	
Neutrophil-to-lymphocyte ratio	4.50 (2.83–7.55)	4.64 (2.81–8.13)	4.44 (2.84–7.40)	.153
No. available	7822	2291	5531	
Platelet count, $\times 10^9$/L	186 (147–240)	180 (141–233)	189 (149–244)	<.001
No. available	7873	2307	5566	
Hemoglobin, g/dL	14.1 (12.9–15.1)	13.8 (12.5–14.9)	14.2 (13.1–15.1)	.019
No. available	7881	2309	5572	
Biochemistry				
Sodium (mmol/L)	137 (135–140)	137 (135–140)	137 (135–139)	.003
No. available	7823	2290	5533	
Creatinine (mg/dL)	0.90 (0.73–1.12)	0.92 (0.75–1.21)	0.89 (0.73–1.10)	<.001
No. available	7860	2304	5556	
eGFR (CKD-EPI)	81.9 (61.0–95.6)	77.2 (52.8–92.7)	83.7 (65.3–96.6)	<.001
No. available	7860	2304	5556	
LDH (U/L)	312 (243–411)	289 (223–395)	320 (251–417)	<.001
No. available	6862	1940	4922	
LDH > 400 (U/L), no./total no. (%)	1864/6862 (27.2)	467/1940 (24.1)	1397/4922 (28.4)	<.001
AST (U/L)	36 (26–54)	32 (23–47)	38 (27–56)	<.001

Table 2 (*Continued*)

	Total (N = 7915)	Early-presenting (n = 2324)	Late-presenting (n = 5591)	*p*
No. available	6143	4661	4387	
ALT (U/L)	30 (20–48)	26 (18–40)	32 (21–51)	<.001
No. available	7448	2129	5319	
AST/ALT ratio	1.18 (0.91–1.54)	1.25 (0.95–1.65)	1.15 (0.9–1.5)	<.001
No. available	6009	1704	4305	
Venous lactate > 2 mmol/L	1.5 (1.1–2.1)	1.5 (1.1–2.2)	1.5 (1.0–2.1)	.013
No. available	3664	1005	2659	
Procalcitonin (ng/mL), median (IQR)	0.10 (0.05–0.20)	0.11 (0.05–0.24)	0.10 (0.05–0.19)	<.001
No. available	3936	1075	2861	
Ferritin (ng/mL), median (IQR)	639 (309–1238)	493 (250–1022)	694 (331–1328)	<.001
No. available	2896	772	2124	
CRP (mg/dL), median (IQR)	5.69 (1.81–12.2)	4.6 (1.30–11.14)	6.20 (2.12–12.62)	<.001
No. available	7561	2207	5354	
CRP $\geq$ 10 mg/dL	2424/7561 (32.1)	635/2207 (28.8)	1789/5354 (33.4)	<.001
Interleukin 6 (pg/mL), median (IQR)	31.9 (11.0–64.5)	34.2 (9.7–66.3)	30.5 (11.9–64.0)	.773
No. available	1128	265	863	
Coagulation-related parameters, median (IQR)				
D-dimer (ng/mL)	588 (341–1044)	620 (342–1218)	577 (340–989)	.001
No. available	6115	1625	4490	
Fibrinogen (mg/dL)	620 (500–739)	587 (500–700)	637 (500–740)	<.001
No. available	5073	1473	3600	
Lung infiltrates on chest X-ray	6996/7853 (89.1)	1904/2302 (82.7)	5092/5551 (91.7)	<.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; eGFR (CKD-EPI) = estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation; LDH = lactate dehydrogenase; PCR = polymerase chain reaction; qSOFA = quick Sepsis Related Organ Failure Assessment; SpO_2/FiO_2 = oxygen saturation to fraction of inspired oxygen ratio.

remained significant and with a higher hazard ratio. On the other hand, D-dimer lost significance in the EP group while it remained significant in the LP group. The rest of the variables remained significant in both groups with variations in their hazard ratio that were more noticeable with age and hemoglobin (Fig. 4).

Discussion

In this nationwide cohort study, we show that DEOS to hospital admission is an independent protective factor of in-hospital death in COVID-19 patients. We also demonstrate that risk factors for in-hospital mortality due to COVID-19 change throughout the course of the disease. This was especially evident with CCI which remained significant only in the EP group, and on the other hand, D-dimer which was only significant in the LP group.

To our knowledge, no multicenter study has pointed DEOS to hospital admission as an independent predictor of in-hospital mortality and no previous work has focused prediction models according to the timeframe of the course of COVID-19 and [30,31]. We show for the first time in a large multicenter study with a huge sample size that lower DEOS to hospital admission is an independent risk factor for hospital mortality. Azoulay et al. showed for the first time that lower DEOS to hospitalization was an independent predictor of in-hospital mortality but their population was limited to a small cohort of patients in the intensive care setting[32]. García-Vidal et al. showed that lower DEOS is independently associated with higher mortality in hospital-admitted COVID-19 patients, but this study was limited to one institution[33]. We all agree that this finding could be related with a higher viral load or a lower capability of the host to control the viral replication as previous works have shown that a higher viral load at hospital admission is related to a shorter DEOS and a higher in-hospital mortality[34,35]. However, the authors recently showed that this association was independent of the value of the Ct upon admission[36].

We believe that previous works have failed to identify this association for two reasons. First, DEOS is a subjective variable. Other studies did not exclude from the analysis patients with cognitive impairment (who are limited to properly self-report their symptoms) and these patients account for a large proportion of COVID-19 deaths and would interfere with the results. Second, we studied a more homogeneous clinical cohort and excluded patients with late viral shedding but with a clinical presentation not related to COVID-19. This was implemented in the study method by establishing the inclusion criterion of a DEOS to admission of less than fifteen days. This decision took into account previously published works that reported a median time from symptoms onset to ARDS and intensive care admission of 9–12 days and 10.5–12 days, respectively[11,12] and viral shed-

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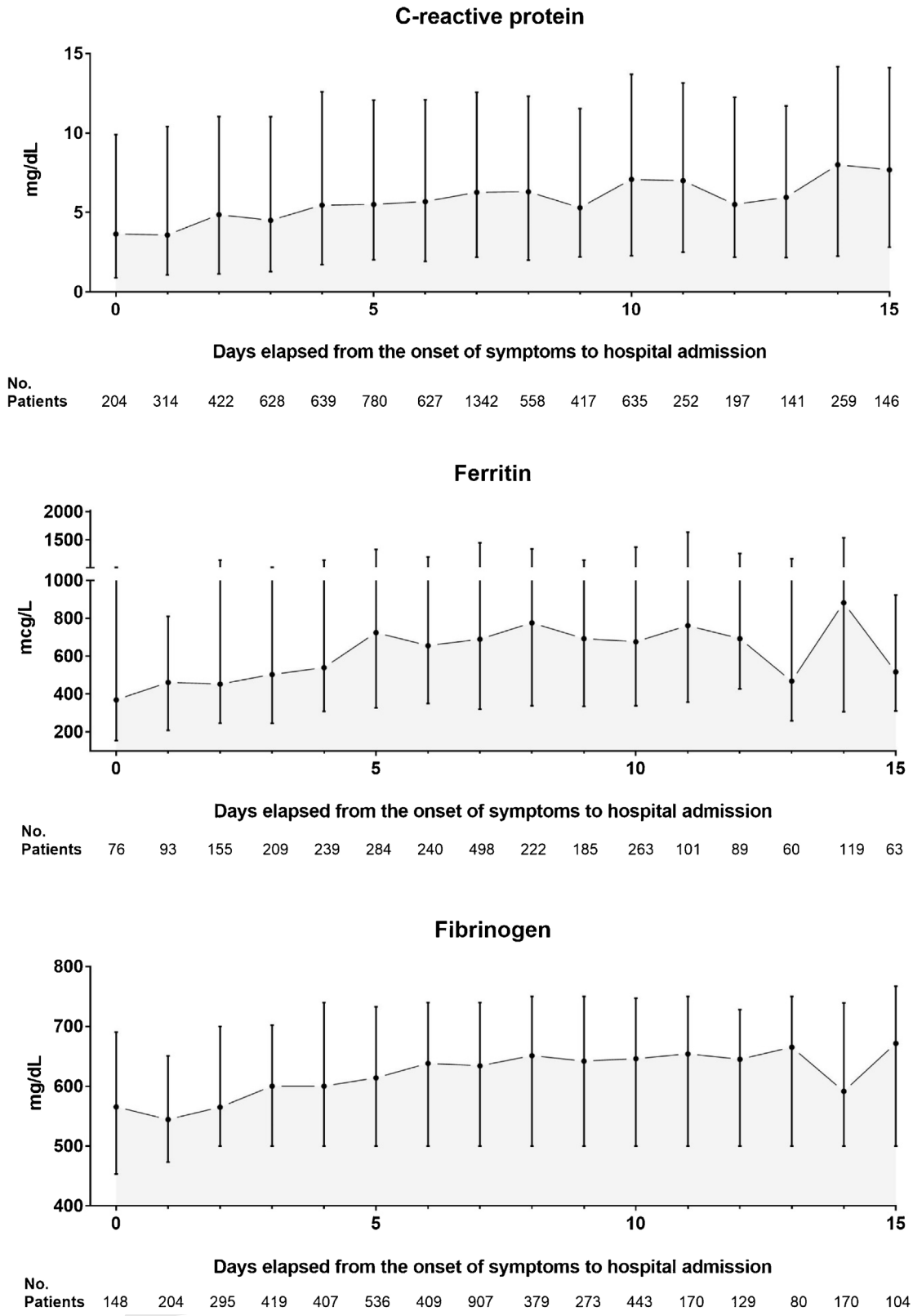

Figure 2 Evolution of laboratory markers of systemic inflammation at hospital admission according to days elapsed from the onset of symptoms to hospital admission.

For each day elapsed from the onset of symptoms to hospital admission, there is a significant increase in the biochemical markers of systemic inflammation upon admission: +0.15 mg/dL for C-reactive protein (95% CI 0.01—0.2; $p < .001$), +21.8 mcg/L for ferritin (95% CI 10.6–32.9; $p < .001$), and +3.34 mg/dL for fibrinogen (95% CI 1.34–5.34; $p = .001$).

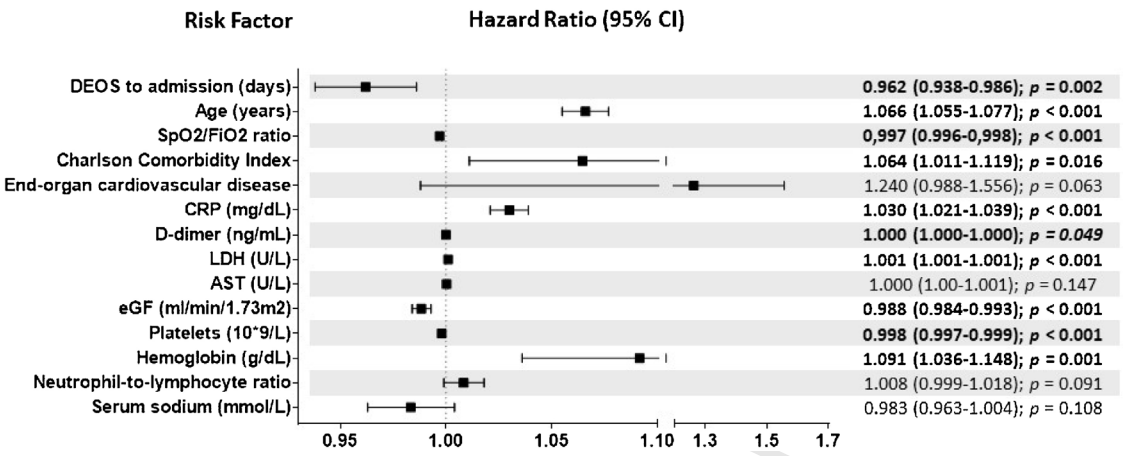

Figure 3 Risk factors of in-hospital death analyzed by means of a multivariate Cox regression analysis.
Hazard ratios values shown for each unit increase (indicated with parentheses), when appropriate.
AST = aspartate aminotransferase; CRP = C-reactive protein; **DEOS** = days elapsed from the onset of symptoms; eGFR = estimated glomerular filtration rate measured using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; LDH = lactate deshydrogenase; SpO_2/FiO_2 = oxygen saturation to fraction of inspired oxygen ratio.

ding that commonly lasts for more than 15 days, even in patients without severe disease[37]. Therefore, we included patients who were hospitalized in the period in which the main COVID-19 related complications (ARDS) occur and excluded patients with a positive SARS-CoV-2 test but who were hospitalized for another reason.

Previous works have found several independent risk factors for COVID-19 in-hospital mortality. Some of these factors, such as age, male sex or comorbidity, are intrinsic to patients' baseline characteristics and therefore static over time[11,13,38,39]. However, these can have different impact on different stages of COVID-19, and as we have shown, the Charlson Comorbidity Index was only significant in the EP group. Other factors, such as LDH, D-dimer, CRP, or IL-6 values at admission[11,40,41], are biochemical parameters that vary over the course of the disease and are thus largely dependent on the DEOS to hospital admission and their variation over time can be more valuable that their isolated value on admission. This way, D-dimer on admission, a recognized prognostic factor of COVID-19 mortality[11,42], was only independently associated with a higher mortality in the LP group.

The strengths of our study include the fact that it is a multicenter study that accurately represents COVID-19 patients in real world clinical practice and its large sample size with a high number of events, which make it suitable for analyzing the outcome. However, our work has some limitations. Above all, the patients included in our cohort were not vaccinated and it has been shown that SARS-CoV2 vaccination is highly effective in preventing COVID-19 related deaths[43,44]. Therefore, our results cannot be extrapolated to most patients admitted at present with COVID-19. Additionally, there is no consensus on any clinical or biochemical thresholds to define the different stages of COVID-19. Therefore, we differentiated between the EP and LP groups mainly based on our best clinical criteria. In addition, several variables of interest that show a time-dependent pattern, such as ferritin or IL-6 (Appendix Fig. 2 in Supplementary material), had a high number of missing values and their role in the prediction model might be undervalued. Lastly, we excluded patients with dementia or those who were severely dependent to ensure the patient was capable of self-reporting the days elapsed from symptoms onset[19], a fact that limits our findings to a specific subgroup of COVID-19 patients without these conditions.

Our findings have relevant implications. Firstly, our results confirm that lower DEOS to hospital admission is a risk factor for in-hospital death in COVID-19 patients. It has been shown that clinicians take DEOS into account when deciding hospital admission, and although our work is not designed nor capable to demonstrate this clinical decision, it may explain the concerns behind this practice[45]. Although as previously mentioned our results are limited to unvaccinated populations, our findings may still be of use in populations with low immunogenicity of COVID-19 vaccines (especially solid organ transplant recipients and patients with haematological malignancy)[46]. Ultimately, we claim that further studies addressing the prognostic factors of COVID-19 complications should stratify their cohorts or select patients who are in a similar timeframe of the disease. COVID-19 has different pathophysiological stages over time[2,5] and thus it is difficult for one prediction model to anticipate COVID-19 mortality at all stages.

Further works may elucidate some of the issues addressed herein. First, better identification of mortality predictors early in the course of COVID-19 are needed to help elucidate which patients would benefit most from longer in-hospital monitoring. Second, future research will surely refine COVID-19 timeframes with immunological and biochemical parameters that better reflect the underlying physiopathology of COVID-19. Finally, it would also be of interest to better fit future prediction models by including laboratory values with their variation in the first 24–48 h after admission instead of the static—and not always reliable—values at admission.

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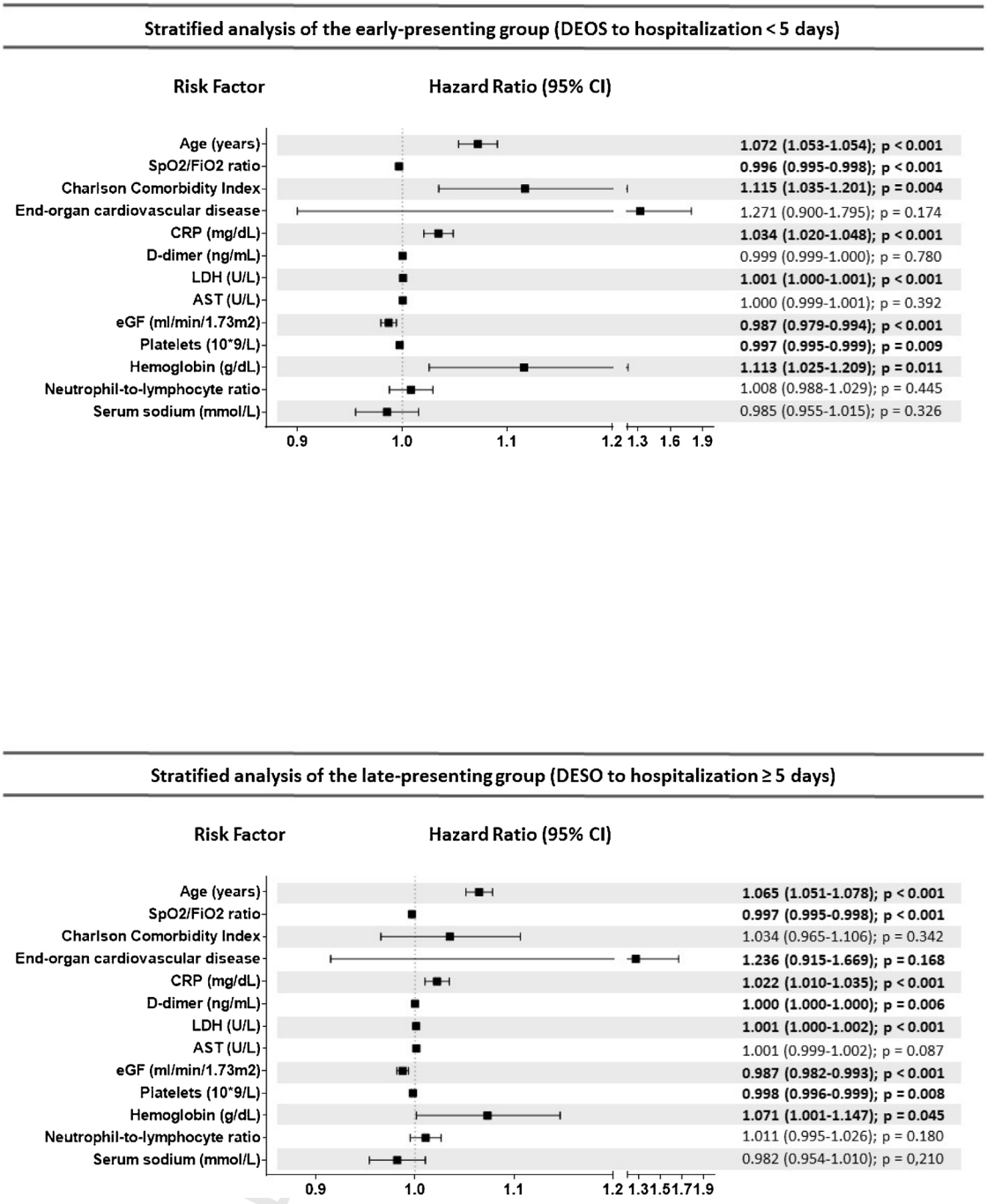

Figure 4 Risk factors of in-hospital death analyzed with a sensitivity analysis of the Cox regression multivariate model in early- and late-presenting groups.
Hazard ratios shown for each unit increase (indicated with parentheses) when appropriate.
AST = aspartate aminotransferase; CRP = C-reactive protein; DEOS = days elapsed from symptoms onset; eGFR = estimated glomerular filtration rate; LDH = lactate deshydrogenase; SpO_2/FiO_2 = oxygen saturation to fraction of inspired oxygen ratio.

Conclusion

COVID-19 patients hospitalized early in the disease course have a higher risk of mortality, with a 4,3% risk reduction with each day elapsed from symptom onset to hospitalization, a fact that should be considered in the clinical decision making. We also show that the dynamic course of COVID-19 over time modifies the significance of different prognostic factors of in-hospital mortality and consequently future studies should be addressed within a prespecified timeframe of the disease.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rceng.2023.03.006.

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