Age-Adjusted Endothelial Activation and Stress Index for Coronavirus Disease 2019 at Admission Is a Reliable Predictor for 28-Day Mortality in Hospitalized Patients With Coronavirus Disease 2019

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Background: Endothelial Activation and Stress Index (EASIX) predict death in patients undergoing allogeneic hematopoietic stem cell transplantation who develop endothelial complications. Because coronavirus disease 2019 (COVID-19) patients also have coagulopathy and endotheliitis, we aimed to assess whether EASIX predicts death within 28 days in hospitalized COVID-19 patients.

Methods: We performed a retrospective study on COVID-19 patients from two different cohorts [derivation ($n = 1,200$ patients) and validation ($n = 1,830$ patients)]. The endpoint was death within 28 days. The main factors were EASIX [(lactate dehydrogenase * creatinine)/thrombocytes] and aEASIX-COVID (EASIX * age), which were $\log_2$-transformed for analysis.

Results: $\log_2$-EASIX and $\log_2$-aEASIX-COVID were independently associated with an increased risk of death in both cohorts ($p < 0.001$). $\log_2$-aEASIX-COVID showed a good predictive performance for 28-day mortality both in the derivation cohort (area under the receiver-operating characteristic = 0.827) and in the validation cohort (area under the receiver-operating characteristic = 0.820), with better predictive performance than $\log_2$-EASIX ($p < 0.001$). For $\log_2$ aEASIX-COVID, patients with low/moderate risk (<6) had a 28-day mortality probability of 5.3% [95% confidence interval (95% CI) = 4–6.5%], high (6–7) of 17.2% (95% CI = 14.7–19.6%), and very high (>7) of 47.6% (95% CI = 44.2–50.9%). The cutoff of $\log_2$ aEASIX-COVID = 6 showed a positive predictive value

of 31.7% and negative predictive value of 94.7%, and $\log_2$ aEASIX-COVID = 7 showed a positive predictive value of 47.6% and negative predictive value of 89.8%.

Conclusion: Both EASIX and aEASIX-COVID were associated with death within 28 days in hospitalized COVID-19 patients. However, aEASIX-COVID had significantly better predictive performance than EASIX, particularly for discarding death. Thus, aEASIX-COVID could be a reliable predictor of death that could help to manage COVID-19 patients.

Keywords: COVID-19, mortality, clinical prediction rule, blood coagulation disorders, endothelium

INTRODUCTION

Around 80% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients develop mild-to-moderate illness, 15% severe illness, and 5% critical illness, including acute respiratory distress syndrome, septic shock, and multiorgan failure (1). Severe coronavirus disease 2019 (COVID-19) is related to high mortality, mostly in older people with comorbidities such as diabetes and cardiovascular diseases (2). Besides, the excessive hospital demand generated by the COVID-19 pandemic during the first wave caused a high request for intensive care beds in Madrid, Spain (3), affecting the quality of medical care and impacting mortality due to COVID-19 (4).

A deregulated pro-inflammatory response (cytokine storm) usually appears in patients with severe COVID-19, which leads to coagulopathy and endothelial damage with frequent episodes of thromboembolism (1, 5). Widespread endotheliitis with diffuse microcirculatory injury in the lung and other organs (brain, heart, kidneys, gut, and liver) is a central feature of severe COVID-19 (1). This disturbed coagulation is strongly associated with acute respiratory distress syndrome, multiorgan failure, and mortality, which is higher than in patients with COVID-19-unrelated pneumonia (1).

During the COVID-19 pandemic, many biomarkers to predict mortality have been reported (6, 7), including lactate dehydrogenase, creatinine, and thrombocyte count. These three markers are part of the Endothelial Activation and Stress Index (EASIX), a powerful score that was initially developed to predict survival in patients with acute graft vs. host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) (8). Endothelial activation is the common trigger of several complications occurring after allo-HSCT, including transplant-associated microangiopathy, sinusoidal obstruction syndrome, and GVHD (9). In the last years, EASIX has also been validated as a predictor for the development of other allo-HSCT complications, including non-relapse mortality (10, 11), fluid overload (12), and sinusoidal obstruction syndrome (13). This score has also been validated in other hematological malignancies outside of the HSCT setting (14, 15).

Because coagulopathy and endothelial dysfunction are critical in the evolution of patients with COVID-19, we aimed to assess whether the EASIX score can predict 28-day mortality in hospitalized COVID-19 patients.

METHODS

Patients

We performed a retrospective study on consecutively hospitalized patients between March 1 and May 31, 2020 (during the first wave of the COVID-19 pandemic) with a laboratory-confirmed with a laboratory-confirmed SARS-CoV-2 infection by real-time polymerase chain reaction. Our study population consisted of two cohorts from two hospitals in Madrid, Spain, which were previously described:

(i) *Derivation cohort* from Infanta Leonor University Hospital (ILUH) (16, 17). Initially, 1,968 patients were included. However, we discarded 391 patients due to missing values for the EASIX variables and 377 patients due to transfer to another institution within 28 days after hospital admission, resulting in a final study population of 1,200 patients. The Ethics Committee of ILUH (Code ILUH R 027-20) approved the study.

(ii) *Validation cohort* from La Paz University Hospital (LPUH) (18). Initially, 2,226 patients were included. We discarded 396 patients due to missing values for the EASIX variables, resulting in a final study population of 1,830 patients. The Ethics Committee of LPUH (Code PI-4072) approved the study.

The study was conducted according to the Declaration of Helsinki. Written informed consent waiver was obtained from the Ethics Committees due to the retrospective nature of the study. In addition, the database was anonymized for statistical analysis. The research followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement (19).

Clinical Data

Demographic and clinical data were extracted from medical records and managed using Research Electronic Data Capture (REDCap). We included age, sex, smoking habit, comorbidities [chronic heart disease, hypertension, chronic pulmonary disease, asthma, chronic kidney disease, liver disease (cirrhosis), neoplasm, hematological malignancy, obesity, diabetes, and dyslipidemia], laboratory findings, and signs at hospital admission [oxygen saturation, hematocrit, blood counts (lymphocytes, neutrophils, thrombocytes), aspartate aminotransferase and alanine aminotransferase, lactate dehydrogenase, glucose, creatinine, sodium, potassium, and C-reactive protein].

EASIX was calculated according to the previously reported formula [lactate dehydrogenase (IU/L) * creatinine

(mg/dl)/thrombocyte count (10^9 cells/L)] (8). Additionally, we calculated the aEASIX-COVID (age-adjusted EASIX for COVID-19), which incorporates age at COVID-19 diagnosis to the previous formula [EASIX * age (years)]. Age was added to EASIX because it is a significant predictor of mortality in COVID-19 patients (20) and is also an easy variable to obtain at the time of the patient's diagnosis. Both indexes were $\log_2$ transformed.

Outcome Variables

The primary endpoint was 28-day all-cause mortality. The baseline was the date at hospital admission. At the follow-up censoring date (May 31, 2020), the clinical status of the patients was discharged alive, currently hospitalized alive, or dead. When a patient was readmitted during the study period, a single hospital admission episode was considered for the purposes of the analysis.

Statistical Analysis

Quantitative variables were expressed as the median and interquartile range, and categorical variables were shown as absolute count (percentage). Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and the chi-squared or two-tailed Fisher's exact test for categorical variables.

We assessed the risk of death using the survival analysis (Kaplan–Meier and Cox regression analyses). The Kaplan–Meier product-limit method was used to estimate survival probabilities at 28 days, and the log-rank test was used to calculate the differences between groups and trends. Cox proportional-hazards models were used to study the association between risk factors (age, sex, smoking habit, comorbidities, laboratory findings, and signs at hospital admission) and mortality during the first 28 days. Continuous variables (including EASIX and aEASIX-COVID) were $\log_2$-transformed (base-2 logarithms). First, we performed univariate Cox regression analyses. Then, we performed multivariate Cox regression analyses with variables that had a p-value $\leq$ 0.05, missing values $\leq$10%, and low collinearity between them ($r < 0.5$), which were further selected by a stepwise forward selection method (pin < 0.05 and pout < 0.10).

Internal validation of the predictive model was made using 20-fold cross-validation. The predictive performance of death within 28 days of hospital admission for EASIX and aEASIX-COVID was evaluated by examining calibration (Hosmer–Lemeshow test) and discrimination [area under the receiver-operating characteristic (AUROC)] measures. We calculated the prediction error for EASIX and aEASIX-COVID in both cohorts using the Brier score. Differences between AUROC models were assessed using the Delong test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the different deciles of the distribution.

Statistical analysis was performed using Stata/IC 15.1 (StataCorp, Texas, USA) and GraphPad Prism 7.04 (GraphPad Software, Inc., California, USA).

RESULTS

Patient Characteristics

Table 1 shows baseline characteristics of COVID-19 patients, stratified by survival/death within 28 days of hospital admission at ILUH (derivation cohort) and LPUH (validation cohort). In both cohorts, patients who died were significantly older, more frequently male, and presented more comorbidities such as chronic heart disease, hypertension, chronic kidney disease, solid neoplasm, hematological malignancy, diabetes, and dyslipidemia. Besides, patients who died showed significantly lower values of hematocrit, lymphocytes, thrombocytes, and alanine aminotransferase, whereas they had higher values of neutrophils, aspartate aminotransferase, lactate dehydrogenase, glucose, creatinine, potassium, and C-reactive protein. Mortality rate within 28 days was significantly lower in ILUH (derivation cohort, 17.7%) than in LPUH (validation cohort, 22.5%) ($p = 0.001$).

Risk of Death Within 28 Days

$\log_2$ EASIX was associated with a higher risk for death within 28 days in the derivation cohort [adjusted hazard ratio (aHR) = 1.55; $p < 0.001$] and the validation cohort (aHR = 1.41; $p < 0.001$) (**Supplementary Table 1**). Furthermore, $\log_2$ aEASIX-COVID showed slightly higher mortality risk values for 28-day death compared with $\log_2$ EASIX (**Supplementary Table 2**), both in the derivation (aHR = 1.61; $p < 0.001$) and in the validation cohort (aHR = 1.51; $p < 0.001$).

Predictive Performance of Death Within 28 Days

$\log_2$ EASIX presented suitable values of calibration (chi-squared = 11.04; $p = 0.198$; **Figure 1A**), discrimination (AUROC = 0.784; **Figure 1B**), and an acceptable prediction error (Brier score = 0.119) at the derivation cohort. At the validation cohort, $\log_2$ EASIX showed similar predictive performance values to the derivation cohort for calibration (chi-squared = 7.36; $p = 0.498$; **Figure 1C**), discrimination (AUROC = 0.774; **Figure 1D**), and an admissible prediction error (Brier score = 0.141). $\log_2$ EASIX PPV increased with deciles but did not exceed 61% in the derivation cohort and 70% in the validation cohort, and NPV decreased with the increase of the deciles but was not <80% in both cohorts (**Supplementary Table 3**).

$\log_2$ aEASIX-COVID showed better values of predictive performance than $\log_2$ EASIX for calibration and discrimination in the derivation cohort [chi-squared = 3.09 ($p = 0.928$; **Figure 1A**) and AUROC = 0.827 ($p < 0.001$; **Figure 1B**), respectively] and in the validation cohort [chi-squared = 6.66 ($p = 0.574$; **Figure 1C**) and AUROC = 0.820 ($p < 0.001$; **Figure 1D**), respectively]. Moreover, Brier scores of $\log_2$ aEASIX-COVID were slightly lower than those obtained for $\log_2$ EASIX (0.111 for derivation and 0.131 for validation cohorts). Internal validation showed an AUC of 0.832 (95% CI = 0.786–0.849) in the derivation cohort and 0.818 (95% CI = 0.795–0.842) in the validation cohort. $\log_2$ aEASIX-COVID PPV raised with the increase in deciles but did not exceed 67% in the derivation cohort and 72% in the validation cohort. Besides, NPV decreased

TABLE 1 | Baseline characteristics of hospitalized COVID-19 patients, stratified by survival at 28 days after admission.

Characteristic	Survivors	Non-survivors	p-value
A) ILUH (derivation cohort)			
No. patients	988 (82.3%)	212 (17.7%)	–
Age, median (IQR)	64 (52–77)	82 (72–87)	**<0.001**
Sex (male)	562 (65.9%)	152 (71.7%)	**<0.001**
Comorbidities			
Chronic heart disease	182 (18.7%)	90 (42.5%)	**<0.001**
Hypertension	486 (49.9%)	152 71.7%)	**<0.001**
Chronic pulmonary disease	106 (10.9%)	50 (23.9%)	**<0.001**
Asthma	85 (8.7%)	11 (5.2%)	0.052
Chronic kidney disease	50 (5.1%)	30 (14.3%)	**<0.001**
Liver cirrhosis	14 (1.4%)	7 (3.4%)	0.062
Neoplasm	32 (3.4%)	29 (12.7%)	**<0.001**
Hematological malignancy	18 (1.9%)	13 (5.6%)	**0.004**
Obesity	154 (18.6%)	26 (15.0%)	0.327
Diabetes	249 (21.4%)	73 (31.6%)	**0.001**
Dyslipidemia	220 (22.7%)	67 (31.8%)	**0.005**
Smoker	50 (7.4%)	9 (7.7%)	0.850
Laboratory findings and signs			
Oxygen saturation in room air (%)	95 (92–97)	90 (82–93)	**<0.001**
Hematocrit (%)	41.5 (38.4–44.2)	39.4 (35.0–43.7)	**<0.001**
Lymphocyte count (cells/μl)	1,000 (800–1,400)	800 (500–1,100)	**<0.001**
Neutrophil count (cells/μl)	4,800 (3,500–6,900)	5,900 (3,800–8,450)	**<0.001**
Thrombocyte count (x 10^9 cells/L)	212 (165–275)	187 (137–264)	**<0.001**
Aspartate Aminotransferase (IU/L)	37 (27–53)	47 (31–71)	**<0.001**
Alanine Aminotransferase (IU/L)	36 (26–56)	31 (22–48)	**<0.001**
Lactate dehydrogenase (IU/L)	255 (207–327)	353 (265–480)	**<0.001**
Glucose (mg/dL)	109 (98–132)	135 (110–167)	**<0.001**
Creatinine (mg/dL)	0.99 (0.80–1.20)	1.31 (1.03–1.94)	**<0.001**
Sodium (mEq/L)	139 (136–141)	138 (136–142)	0.715
Potassium (mEq/L)	4.2 (3.9–4.6)	4.4 (4.0–4.8)	**0.004**
C-reactive Protein (mg/L)	60.9 (22.7–122.0)	119.8 (56.2–208.7)	**<0.001**
B) LPUH (validation cohort)			
No. patients	1,418 (77.5%)	412 (22.5%)	–
Age, median (IQR)	65 (53–77)	81 (74–87)	**<0.001**
Sex (male)	745 (52.6%)	264 (64.1%)	**<0.001**
Comorbidities			
Chronic heart disease	281 (19.9%)	161 (36.4%)	**<0.001**
Hypertension	660 (46.7%)	278 (67.5%)	**<0.001**
Chronic pulmonary disease	108 (7.7%)	41 (10.1%)	0.124
Asthma	72 (5.1%)	12 (2.9%)	0.081
Chronic kidney disease	95 (6.7%)	80 (19.5%)	**<0.001**
Liver cirrhosis	15 (1.1%)	7 (1.7%)	0.305
Neoplasm	151 (10.7%)	86 (21.0%)	**<0.001**
Hematological malignancy	88 (6.2%)	53 (12.9%)	**<0.001**
Obesity	238 (17.2%)	67 (16.8%)	0.880
Diabetes	284 (20.1%)	125 (30.5%)	**<0.001**
Dyslipidemia	530 (37.6%)	212 (51.6%)	**<0.001**
Smoker	100 (7.3%)	36 (9.8%)	0.111
Laboratory findings and signs			
Oxygen saturation in room air (%)	91.9 (75.9–95.3)	92.4 (82.2–96.4)	0.258
Hematocrit (%)	42.3 (38.9–45.1)	40.5 (36.3–44.4)	**<0.001**

(Continued)

TABLE 1 | Continued

Characteristic	Survivors	Non-survivors	p-value
Lymphocyte count (cells/µl)	1,130 (790–1,690)	710 (470–1,060)	**<0.001**
Neutrophil count (cells/µl)	3,845 (2,830–5,550)	6,135 (3,870–9,085)	**<0.001**
Thrombocyte count (x 10^9 cells/L)	249 (191–322)	217 (161–290)	**<0.001**
Aspartate Aminotransferase (IU/L)	31 (21–50)	41 (26–60)	**<0.001**
Alanine Aminotransferase (IU/L)	32 (21–55)	27 (18–45)	**<0.001**
Lactate dehydrogenase (IU/L)	286 (226–361)	385 (293–514)	**<0.001**
Glucose (mg/dl)	99 (88–116)	115 (97–149)	**<0.001**
Creatinine (mg/dl)	0.77 (0.63–0.93)	1.02 (0.77–1.49)	**<0.001**
Sodium (mEq/L)	139 (137–142)	140 (136–143)	0.060
Potassium (mEq/L)	4.0 (3.7–4.3)	4.1 (3.7–4.5)	**0.008**
C-reactive Protein (mg/L)	32.7 (6.5–96.5)	126.8 (56.4–209.6)	**<0.001**

Statistics: Values are expressed as median and interquartile range for continuous variables and absolute count (percentage) for categorical variables. p-values were calculated by chi-squared or two-tailed Fisher's exact test for categorical variables and Mann–Whitney test for continuous variables. Significant differences are shown in bold. Abbreviations: p-value, level of significance; IU, international units; ul, microliter; ILUH, Infanta Leonor University Hospital; LPUH, La Paz University Hospital.

with increasing deciles but was not below 80% in both cohorts (**Supplementary Table 4**).

Probability of Death Within 28 Days

We considered the risk of 28-day mortality, joining the two cohorts, in three strata (low/moderate, high, and very high). For $\log_2$ EASIX, 28-day mortality probability values were 7.8% for patients with low/moderate risk (<0), 18.6% for high risk (0–1), and 45.4% for very high risk (>1) (**Figure 2A**). The cutoff of $\log_2$ EASIX = 0 showed a PPV of 29.8% and NPV of 92.2%, and $\log_2$ EASIX = 1 showed a PPV of 45.3% and NPV of 87.4% (**Table 2**). For $\log_2$ aEASIX-COVID, 28-day mortality probability values were 5.3% for patients with low/moderate risk (<6), 17.2% for high risk (6, 7), and 47.6% for very high risk (>7) (**Figure 2B**). The cutoff of $\log_2$ aEASIX-COVID = 6 showed a PPV of 31.7% and NPV of 94.7%, and $\log_2$ aEASIX-COVID = 7 showed a PPV of 47.6% and NPV of 89.8% (**Table 2**). The Kaplan–Meier curve for the 28-day mortality also showed a different evolution of patients according to the different risk strata according to $\log_2$ EASIX (**Figure 2C**) and $\log_2$ aEASIX-COVID (**Figure 2D**).
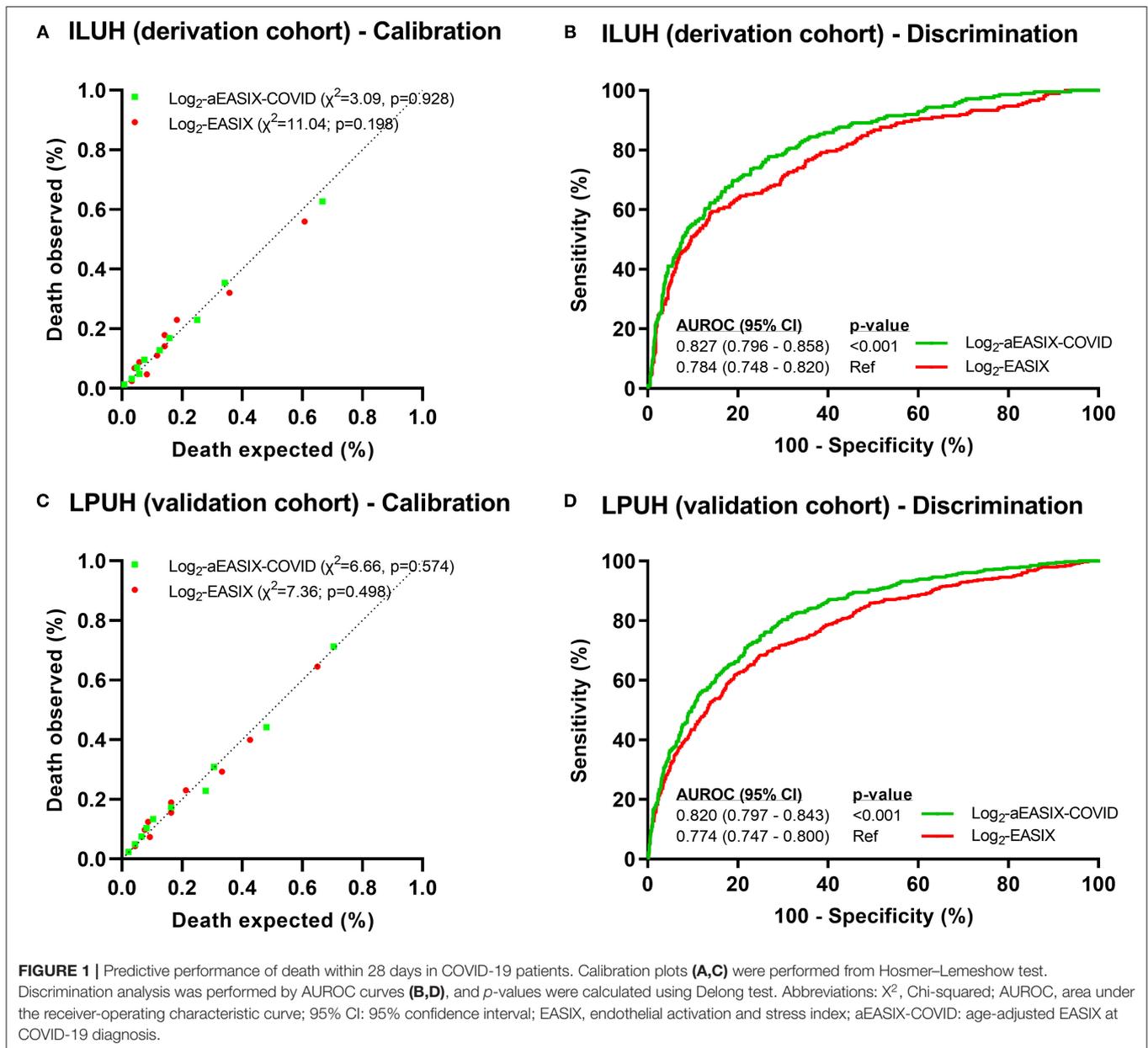
DISCUSSION

We evaluated EASIX for predicting mortality within 28 days in hospitalized COVID-19 patients from two large datasets in Spain. The main findings of our study were as follows: (i) the increase in EASIX values, especially in aEASIX-COVID, was linked to higher 28-day mortality. (ii) EASIX and aEASIX-COVID had a good predictive performance, but only aEASIX-COVID had AUROC >0.8 in the derivation and validation cohorts. (iii) EASIX and aEASIX-COVID were more reliable in predicting patient survival than death because the NPV values were much higher than the PPV values. (iv) EASIX and aEASIX-COVID allowed the stratification of COVID-19 patients into three risk categories of 28-day mortality.

Many predictive scores for mortality in COVID-19 patients have been developed (20, 21). However, most of these predictive scores do not exceed the AUROC of 0.8, including comorbidities related to poor COVID-19 prognosis or variables that are not always available in clinical practice. Besides, these scores require laborious calculations as long as they are based on complex multivariate models. Therefore, we hypothesized that EASIX, a simple score developed for endotheliopathy associated with allo-HSCT, could also predict mortality in COVID-19 patients because endotheliopathy is crucial for its pathophysiology (1).

EASIX was initially developed by Luft et al. as a predictor of survival in patients with acute GVHD after allo-HSCT (8) and later validated to predict mortality related to different post-HSCT complications (10–15). For the development of EASIX, the authors chose three laboratory parameters that were part of the classical diagnostic criteria of thrombotic microangiopathy (creatinine, lactate dehydrogenase, and thrombocyte counts) due to both their simplicity and their association with endothelial dysfunction and microangiopathy (8). Widespread endotheliitis and coagulopathy are also keys in the pathophysiology of COVID-19 (1). Recently, Luft et al. (22) have reported in two cohorts of 100 and 126 patients that EASIX predicts COVID19 outcome and may discriminate patients who need intensive surveillance. Besides, high EASIX values correlated with increased serum values of endothelial (angiopoietin-2, CXCL8, soluble thrombomodulin, and suppressor of tumorigenicity-2) and inflammatory (CXCL9, IL18, and IL18BPa) biomarkers (22). In our study, EASIX showed reasonable accuracy in predicting death within 28 days in hospitalized COVID-19 patients despite its simplicity and the fact that it was developed in a different setting. Both the simplicity and applicability make this score especially useful in healthcare overload and low-resource settings.

Moreover, because age has largely been described as one of the most important predictors of mortality in patients with COVID-19 (20), we postulated that an age-adjusted EASIX (aEASIX-COVID) might increase its predictive performance for 28-day mortality. In our study, the predictive performance

A ILUH (derivation cohort) - Calibration

Log$_2$-aEASIX-COVID (χ^2=3.09, p=0.928)
Log$_2$-EASIX (χ^2=11.04; p=0.198)

B ILUH (derivation cohort) - Discrimination

AUROC (95% CI)	p-value	
0.827 (0.796 - 0.858)	<0.001	Log$_2$-aEASIX-COVID
0.784 (0.748 - 0.820)	Ref	Log$_2$-EASIX

C LPUH (validation cohort) - Calibration

Log$_2$-aEASIX-COVID (χ^2=6.66, p=0.574)
Log$_2$-EASIX (χ^2=7.36; p=0.498)

D LPUH (validation cohort) - Discrimination

AUROC (95% CI)	p-value	
0.820 (0.797 - 0.843)	<0.001	Log$_2$-aEASIX-COVID
0.774 (0.747 - 0.800)	Ref	Log$_2$-EASIX

FIGURE 1 | Predictive performance of death within 28 days in COVID-19 patients. Calibration plots **(A,C)** were performed from Hosmer–Lemeshow test. Discrimination analysis was performed by AUROC curves **(B,D)**, and p-values were calculated using Delong test. Abbreviations: χ^2, Chi-squared; AUROC, area under the receiver-operating characteristic curve; 95% CI: 95% confidence interval; EASIX, endothelial activation and stress index; aEASIX-COVID: age-adjusted EASIX at COVID-19 diagnosis.

of the aEASIX-COVID was significantly superior to the EASIX (initial model) in our two cohorts (derivation and validation) (23). However, EASIX and aEASIX-COVID were more reliable in predicting patient survival than death because NPV values were much higher than PPV values. Furthermore, the predictive performance of aEASIX-COVID for 28-day mortality was similar to Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) (24) and PANDEMYC scores (17), which were both constructed from patients included in our study. However, SEIMC and PANDEMYC scores are more complex to calculate because they are constructed with a higher number of variables (seven to nine variables) than aEASIX-COVID (four variables), and their developments were based on more complex calculations.

Our study presents some limitations. First, this retrospective study only included patients belonging to the first pandemic wave, which was associated with higher mortality rates worldwide. Another limitation could be that aEASIX-COVID relied exclusively on hospitalized patients. Consequently, its applicability in primary care settings, where routine laboratory tests are not usually used, is unknown. Finally, a limitation common to all reported COVID-19 prognostic models is that our study was carried out in Spain, limiting our findings' extrapolation to other countries and healthcare settings. In this regard, the level of hospital saturation generated in the first wave of the COVID-19 epidemic could affect our results (new admissions, number of transfers to other hospitals daily, patient/physician ratio, available intensive care unit beds, among others). Consequently, additional studies are needed to validate
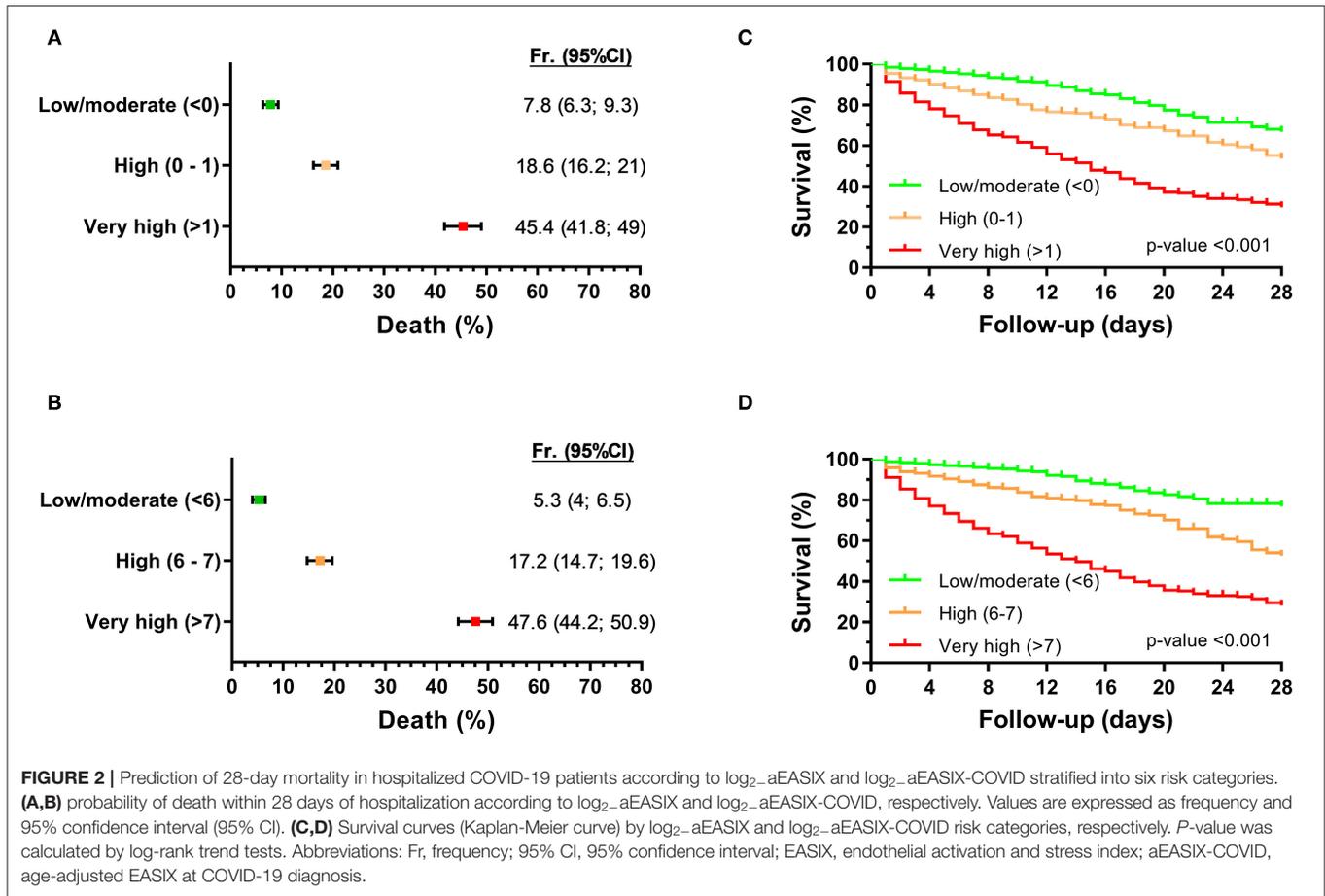
FIGURE 2 | Prediction of 28-day mortality in hospitalized COVID-19 patients according to $\log_2$_aEASIX and $\log_2$_aEASIX-COVID stratified into six risk categories. **(A,B)** probability of death within 28 days of hospitalization according to $\log_2$_aEASIX and $\log_2$_aEASIX-COVID, respectively. Values are expressed as frequency and 95% confidence interval (95% CI). **(C,D)** Survival curves (Kaplan-Meier curve) by $\log_2$_aEASIX and $\log_2$_aEASIX-COVID risk categories, respectively. *P*-value was calculated by log-rank trend tests. Abbreviations: Fr, frequency; 95% CI, 95% confidence interval; EASIX, endothelial activation and stress index; aEASIX-COVID, age-adjusted EASIX at COVID-19 diagnosis.

TABLE 2 | Sensitivity, specificity, PPV, and NPV for predicting 28-day mortality in hospitalized COVID-19 patients according to $\log_2$_EASIX and $\log_2$-aEASIX-COVID deciles.

Cutoff	Risk of 28-day death	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
log2 EASIX					
0	Low/moderate	84.1 (81.0–86.9)	48.5 (46.5–50.6)	29.8 (27.7–32.0)	92.2 (90.6–93.6)
1	Very high	53.8 (49.8–57.8)	83.2 (81.6–84.6)	45.3 (41.7–49.0)	87.4 (86.0–88.8)
log2 aEASIX-COVID					
6	Low/moderate	89.3 (86.6–91.6)	50.2 (48.1–52.2)	31.7 (29.5–34.0)	94.7 (93.4–95.9)
7	Very high	64.3 (60.4–68.0)	81.7 (80.1–83.2)	47.6 (44.2–51.1)	89.8 (88.5–91.0)

Abbreviations: EASIX, Endothelial Activation and Stress Index; aEASIX-COVID, age-adjusted EASIX for COVID-19; PPV, positive predictive value; NPV, negative predictive value; 95% CI, 95% confidence interval.

the diagnostic performance of aEASIX-COVID in different epidemiological contexts. Further complementary studies could include the evaluation of EASIX and aEASIX-COVID for the prediction of cardiovascular and thromboembolic complications (such as pulmonary thromboembolism) in the context of COVID-19.

This study also has several strengths. First, our research has a large sample size and a large number of events, both in the derivation and validation cohorts. Besides, our research adheres to the TRIPOD recommendations. Finally, the aEASIX-COVID score is easy to calculate with normally accessible variables, which would allow rapid decision-making in COVID-19 patients.

CONCLUSION

Both EASIX and aEASIX-COVID were associated with death within 28 days in hospitalized COVID-19 patients. However, aEASIX-COVID had significantly better predictive performance than EASIX, particularly for discarding death. Thus, our findings suggest that aEASIX-COVID could be a reliable predictor of death that could help to manage COVID-19 patients.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study may be available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Infanta Leonor University Hospital Ethics Committee (Code: ILUH R 027-20) and the Ethics Committee of La Paz University Hospital (Code: PI-4072). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SR and PR: funding body. FP-G and SR: study concept, design, statistical analysis, and interpretation of data. PR, JT-M, EJ, MP-B, JC, J-CG, IG-G, and MJ-G: patients' selection and clinical data acquisition. FP-G, RB, and SR: writing of the manuscript. PR, MÁJ-S, and AF-R: critical revision of the manuscript for relevant intellectual content. SR: supervision and visualization. All authors contributed to the article and approved the submitted version.

FUNDING

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.736028/full#supplementary-material

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