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Endothelial Activity and Stress Index (EASIX) Score as a Predictor for Early Severe COVID-Related Mortality

Mahmoud Ahmed Elrefy1, Sabry Shoeib1, Ahmed Abozenah2, Ibrahim A. Kassab3, Alaa Efat1
Department of1 Internal Medicine, Faculty of Medicine, Menoufia University, Egypt, Cairo University Hospitals2, Egypt, Department of 3internal Medicine, Sirs Allyan General Hospital, Menoufia, Egypt
Corresponding author: Ibrahim Abd Elnasser Kassab, **Mobile :01019718443, Email:** ibrahimkassab69@gmail.com

ABSTRACT
Background: Severe COVID-19 often triggers an uncontrolled surge of pro-inflammatory cytokines, leading to endothelial injury that plays a critical role in early mortality.
Objective: This study aimed to estimate endothelial activity and stress index (EASIX) score and find out if there is association between EASIX score and early mortality in adults with severe COVID-19.
Subjects and methods: This retrospective observational analysis study included 200 adult patients diagnosed with severe COVID-19 and admitted to Menoufia University Hospitals between June and November 2021. Patients were divided into two groups: survivors and non-survivors.
Results: EASIX scores were significantly higher in non-survivors indicating a strong association with early COVID-19–related deaths. Significant differences were also noted between the two groups in hemoglobin levels, absolute lymphocyte count, D-dimer, LDH, CRP, ferritin, creatinine, and BUN values.
Conclusion: The EASIX score demonstrated excellent predictive accuracy for early mortality (AUC = 0.981) and can serve as a practical tool for assessing risk in severe COVID-19 patients.
Keywords: COVID-19, Early mortality, EASIX score, D-dimer, LDH.

INTRODUCTION

The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been the most challenging health crisis in recent history, marked by high transmission rates and substantial mortality[1].

By May 2023, approximately 700 million confirmed infections and over 6 million deaths had been reported worldwide[2].

Risk factors for severe disease continue to evolve. Individuals aged 65 years or older, and those with comorbidities such as cardiovascular disorders, chronic lung disease, diabetes, obesity, malignancy, chronic kidney disease, pregnancy, smoking history, or immunosuppression diseases face a heightened risk of severe illness[3]. SARS-CoV-2 invades host cells through angiotensin-converting enzyme 2 (ACE2) receptors via its spike protein[4]. Endothelial cells, which also express ACE2, are susceptible to direct viral entry[5].

Severe COVID-19 is often accompanied by endothelial injury, excessive cytokine release, immune dysregulation, and vascular damage, ultimately resulting in multi-organ failure[6].

Given this pathophysiological background, endothelial dysfunction has emerged as a central driver of severe COVID-19 complications. This study investigated the role of the Endothelial Activation and Stress Index (EASIX) in predicting early mortality in severe COVID-19 patients[5,7].

SUBJECTS AND METHODS

This retrospective observational research was carried out in The Intensive Care Unit (ICU) of Menoufia University over a six-month period, from June to November 2021. A total of 200 adult patients (156 males and 44 females) with laboratory-confirmed COVID-19 infection were enrolled. Participants were categorized into two groups: Group A consisted of survivors, while group B included non-survivors.

Medical records were reviewed by trained healthcare professionals using standardized data collection forms, and all entries were verified by the research team to ensure completeness and accuracy. Patient anonymity was maintained throughout the study.

Eligible participants were adults aged 18 years or older, with COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR), and classified as severe or critical according to World Health Organization (WHO) criteria. Severe disease was defined as having a respiratory rate ≥30/min, oxygen saturation ≤93%, a PaO_2/FiO_2 ratio <300 mmHg, or radiological evidence of lung infiltrates involving >50% of the lung fields. Critical cases were those presenting with acute respiratory distress syndrome (ARDS), septic shock, or multiple organ failure. All patients were managed according to WHO treatment protocols[8]. Individuals younger than 18 years, or those with ICU stays shorter than 24 hours or longer than seven days, were excluded.

Ethical approval: Ethical clearance was obtained from The Local Ethical Committee of the Faculty of Medicine, Menoufia University (IRB: 6/2024 INTM 34). Written informed consentswere provided by all participants or their legal representative prior to inclusion. The research followed The Declaration of Helsinki through its execution.

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Statistical analysis

Data were initially recorded in Microsoft Excel 2016 and analyzed using IBM SPSS Statistics for Windows, version 25.0. Normality of distribution was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables were expressed as mean ± SD, while categorical variables were summarized as frequencies and percentages. For comparisons, the Student's t-test was used for continuous variables, and the Chi-square test for categorical variables. Receiver Operating Characteristic (ROC) curves were used to assess the diagnostic performance of key clinical and laboratory parameters. P value ≤ 0.05 was deemed significant.

RESULTS

Table (1) summarized the baseline demographic, clinical, and laboratory data of the studied patients. The mean age of non-survivors (69 years) was significantly higher than that of survivors (57 years) ($p < 0.05$). Non-survivors showed significantly higher prevalence of diabetes, hypertension, fever, cough, chest pain, dyspnea, increased respiratory rate, greater oxygen requirement, and elevated inflammatory markers (CRP, LDH, D-dimer& ferritin), BUN, creatinine, and EASIX score ($p < 0.05$). In contrast, they had significantly lower hemoglobin concentrations and lymphocyte counts ($p < 0.05$) (Table 2).

Table (1): Baseline characteristics of studied patients(n = 200)

Variable	N (%)
Age (years)Mean ± SD	**65.74 ± 8.83**
Sex: Male	**156 (78.0%)**
Smoking	**41 (20.5%)**
DM	**82 (41.0%)**
HTN	**116 (58.0%)**
Fever	**156 (78 %)**
Cough	**115 (57.5%)**
Dyspnea	**145 (72.5%)**
Chest pain	**18 (9.0%)**
Vomiting, Nausea	**26 (13.0%)**
Diarrhea	**26 (13.0%)**
Musculoskeletal symptoms	**29 (14.5%)**
Neurological symptoms	**63 (31.5%)**
Oxygen Saturation (%)	**83.81 ± 5.66**
Respiratory Rate (breaths/min)	**31.60 ± 2.64**
Pulse (bpm)	**94.36 ± 21.18**
HB (g/dl)	**10.97 ± 2.16**
RBCs (10^6/ul)	**5.03 ± 0.60**
WBCs (10^3/ul)	**7.49 ± 2.00**
Platelets (10^3/ul)	**275.28 ± 75.72**
Lymphocyte Absolute Count (10^3/uL)	**0.96 ± 0.39**
CRP	**64.25 ± 57.36**
S.ferritin	**332.70 ± 96.37**
D.dimer	**822.74 ± 1431.68**
Albumin (g/dL)	**3.71 ± 0.71**
AST (U/L)	**55.21 ± 4.43**
ALT (U/L)	**62.08 ± 3.02**
Total Bilirubin (mg/dL)	**1.14 ± 0.05**
Direct Bilirubin (mg/dL)	**0.78 ± 0.1**
Albumin (g/dL)	**3.71 ± 0.7**
LDH	**480.75 ± 96.27**
INR	**1.37 ± 0.3**
Fibrinogen (mg/dL)	**396.54 ± 15.57**
aPTT (sec)	**36.99 ± 7.01**
BUN (mg/dL)	**40.21 ± 5.41**
Creatinine	**1.66 ± 0.38**
EASIX Score	**10.43 ± 2.85**
Mortality	**144 (72.0%)**

Table (2): Correlation of early mortality and demographic, clinical data and laboratory investigations (n = 200)

Variable	Survivors (n = 56) (N %)	Non-survivors (n = 144) (N %)	Test.of significance	P-value
Age (years)Mean ± SD	57.36 ± 5.18	69.00 ± 7.74	t = 10.379	<0.001**
Sex: Male	40 (71.4%)	116 (80.6%)	χ^2 = 1.957	0.162
Smoking	6 (10.7%)	35 (24.3%)	χ^2 = 4.570	0.033*
DM	6 (10.7%)	35 (24.3%)	χ^2 = 7.330	<0.001*
HTN	10 (17.9%)	48 (33.3%)	χ^2 = 7.925	<0.001**
Fever	33 (58.9%)	123 (85.4%)	χ^2 = 14.978	<0.001**
Cough	26 (46.4%)	89 (61.8%)	χ^2 = 3.297	0.0694
Dyspnea	33 (58.9%)	112 (77.8%)	χ^2 = 7.185	0.007*
Chest pain	0 (0.0%)	18 (12.5%)	χ^2 = 7.692	0.006*
Vomiting, Nausea	5 (8.9%)	21 (14.6%)	χ^2 = 1.14	0.286
Diarrhea	7 (12.5%)	19 (13.2%)	χ^2 = 0.017	0.896
Musculoskeletal symptoms	12 (21.4%)	17 (11.8%)	χ^2 = 3.012	0.083
Neurological symptoms	12 (21.4%)	51 (35.4%)	χ^2 = 3.656	0.056
Oxygen Saturation (%) (Mean ± SD)	85.08 ± 3.98	83.32 ± 6.13	t = 3571	0.210
High flow nasal oxygen (Mean ± SD)	45 (80.4%)	85 (59.0%)	t = 8.06	0.005*
Mechanical Ventilation (Mean ± SD)	27 (48.2%)	115 (79.9%)	t = 19.610	<0.001**
Respiratory Rate (breaths/min)(Mean ± SD)	28.30 ± 1.33	32.88 ± 1.76	t = 72.00	<0.001**
Pulse (bpm) (Mean ± SD)	94.80 ± 22.48	94.18 ± 20.74	t = 3917	0.755
HB (g/dl)) (Mean ± SD)	12.67±1.47	11.39±2.04	t = 2431	<0.001**
RBCs (10^6/uL) (Mean ± SD)	5.02±0.64	5.04 ± 0.58	t = 3999	0.930
WBCs (10^3/uL)) (Mean ± SD)	7.82±0.18	7.35±1.91	t = 3696	0.145
Platelets (10^3/uL)) (Mean ± SD)	265.11±8.71	279.23±7.60	t = 3597	0.237
Lymphocyte Absolute Count (10^3/uL) (Mean ± SD)	1.15±0.15	0.88±0.18	t = 2872	0.002*
CRP) (Mean ± SD)	14.68±2.12	83.53±6.66	t = 117.00	<0.001**
S.ferritin) (Mean ± SD)	430.55±7.86	294.65±7.79	t = 807.00	<0.001**
D.dimer) (Mean ± SD)	5.16±1.27	1140.68±177.58	t = 3.00	<0.001**
Albumin (g/dL) (Mean ± SD)	3.64 ± 0.73	3.74 ± 0.70	t = 3702	0.369
AST (U/L)(Mean ± SD)	54.97 ± 4.25	55.30 ± 4.58	t = 3967	0.997
ALT (U/L) (Mean ± SD)	61.55 ± 3.44	62.29 ± 3.96	t = 4030	0.859
Total Bilirubin (mg/dL) (Mean ± SD)	1.24 ± 0.18	1.10 ± 0.10	t = 3378	0.075
Direct Bilirubin (mg/dL) (Mean ± SD)	0.82 ± 0.10	0.76 ± 0.12	t = 3710	0.382
LDH (Mean ± SD)	318.70±8.95	543.76±91.35	t = 747	<0.001**
INR (Mean ± SD)	1.30 ± 0.39	1.40 ± 0.35	t = 3412	0.092
Fibrinogen (mg/dL) (Mean ± SD)	385.23 ± 22.30	400.93 ± 12.96	t = 3695	0.360
aPTT (sec)(Mean ± SD)	36.50 ± 6.45	37.18 ± 7.23	t = 3815	0.553
BUN (mg/dL) (Mean ± SD)	25.16 ± 1.98	46.06 ± 3.51	t = 2287	<0.001**
Creatinine) (Mean ± SD)	0.69 ± 0.10	2.03 ± 0.46	t = 714	<0.001**
EASIX Score) (Mean ± SD)	1.62 ± 0.44	10.48 ± 1.81	t = 153	<0.001**

(χ2): Chi-square Test**,** t: independent sample test, **p**: p-value for comparing the studied group***:** p value<0.05 is significant * ****:** p value<0.001 is highly significant.

The EASIX score demonstrated excellent predictive value for mortality with AUC > 0.98, high sensitivity, and specificity. D-dimer achieved perfect diagnostic accuracy (AUC = 1.000), while creatinine, ferritin, and LDH also showed strong performance (AUC > 0.9). Hemoglobin, lymphocyte count, and BUN had moderate predictive ability (AUCs 0.64–0.71), displaying high sensitivity but lower specificity (Table 3 & figure 1).

Table (3): Prognostic performance for EASIX score to predict early mortality

	AUC	P-value	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
EASIX Score	**0.981**	**<0.001****	**0.866 - 0.989**	**≥2.37**	**97.9%**	**91.4%**	**96.5%**	**94.6%**

AUC: Area Under a Curve, **p-value:** Probability value, **NPV:** Negative predictive value, **PPV:** Positive predictive value,
:** Statistically significant at p ≤ 0.05, *:** Statistically highly significant at p ≤ 0.001, **CI:** confidence interval

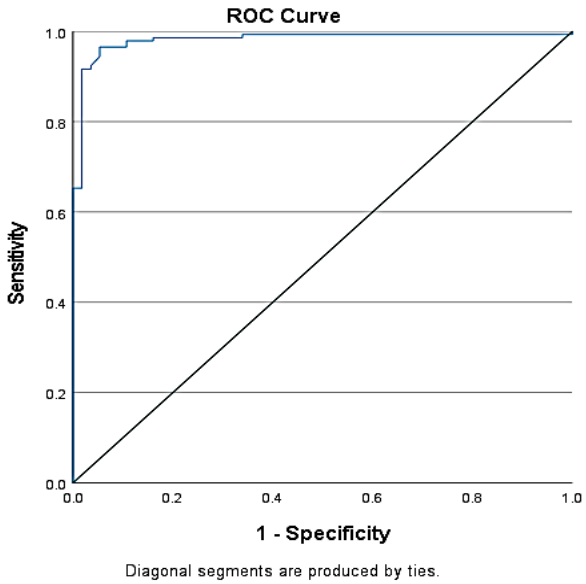

Figure (1): Roc curve analysis.

Multivariate and univariate analyses identified age, fever, oxygen therapy, hemoglobin, ferritin, and EASIX score as independent predictors of poor outcomes, each showing strong and statistically significant associations (Table 4).

Table (4): Univariate and multivariate logistic regression analysis for variables affecting early mortality

	Univariate		Multivariate	
	HR(95%C.I)	**p value**	**HR(95%C.I)**	**p value**
Age	**1.374(1.250 –1.510)**	**<0.001****	**1.326(1.062-1.655)**	**0.013***
Smoking	**2.676(1.057-6.772)**	**<0.001****	**-**	**-**
DM	**3.979(1.906-8.304)**	**0.038***	**-**	**-**
HTN	**3.600(1.885-6.876)**	**<0.001****	**-**	**-**
Fever	**2.659(1.481-4.774)**	**<0.001****	**7.656(1.828-32.060)**	**0.005***
Cough	**1.063(0.735-1.538)**	**<0.001****	**-**	**-**
Dyspnea	**2.439(1.259-4.727)**	**0.747**	**-**	**-**
Chest pain	**1.000(0.000)**	**0.008***	**-**	**-**
Respiratory rate	**1.000(0.000)**	**<0.001****		
High flow nasal oxygen therapy	**0.352(0.168-0.737)**	**0.989**	**0.005(0.000-0.089)**	**0.000***
Mechanical ventilation	**4.259(2.193-8.272)**	**0.006***	**232.031(10.197-5279.695)**	**0.001***
HB	**0.710(0.599-0.842)**	**<0.001****	**0.209(0.049-0.892)**	**0.035***
Lymphocytes	**0.139(0.056-0.347)**	**<0.001****	**-**	**-**
D. dimer	**1.377(0.000-33409)**	**<0.001****	**-**	**-**
CRP	**1.038(1.020-1.058)**	**<0.001****	**-**	**-**
S. ferritin	**0.981(0.976-0.986)**	**<0.001****	**0.950(0.905-0.997)**	**0.037***
LDH	**1.015(1.011-1.019)**	**0.950**	**-**	**-**
BUN	**1.027(1.011-1.043)**	**<0.001****	**-**	**-**
Creatinine	**2.807(1.661-4.743)**	**<0.001****	**-**	**-**
EASIX Score	**28.542(10.239-79.563)**	**<0.003****	**17.376(1.890-159.757)**	**0.012***

P: P value (probability value), *****Significant as P value ≤0.05, **CI:** Confidence interval, **HR:** Hazard ratio.

DISCUSSION

Sepsis-induced endothelial dysfunction contributes to microcirculatory impairment, increased vascular permeability, inflammation, and oxidative injury all of which worsen multiple organ dysfunction syndrome (MODS). This pathology is linked to glycocalyx degradation, altered nitric oxide (NO) regulation, disruption of intercellular signalling, and upregulation of adhesion molecules alongside inflammatory mediators. During sepsis, endothelial activation elevates reactive species such as NO and reactive oxygen species (ROS), intensifying oxidative stress and vascular injury, thereby promoting MODS [9].

The Endothelial Activation and Stress Index (EASIX), initially designed for thrombotic microangiopathy diagnosis, integrates laboratory parameters that indirectly indicate endothelial function. Higher values reflect more severe endothelial impairment [10].

In this retrospective review of 200 hospitalized COVID-19 patients, mortality reached 72%, particularly among older individuals with preexisting health conditions. Elevated ferritin, CRP, D-dimer, and EASIX scores showed strong associations with death. Gender distribution did not significantly differ between survivors and non-survivors. These findings are in line with findings by **Raimondi *et al.*** [11]. However, several reports suggest male sex as a mortality risk factor in COVID-19 [12,13].

Age was a strong mortality predictor in our analysis, which is consistent with results from **Kouhpayeh**[12], **Sasson**[14]and **Estiri *et al.*** [15], possibly due to age-related immune decline and higher pro-inflammatory cytokine production [16, 17]. Non-survivors had significantly higher prevalence of comorbidities such as diabetes and hypertension ($p < 0.001$), echoing a systematic review of over 310,000 patients from 114 studies [16].

Markers of coagulation and inflammation including ferritin, D-dimer, LDH, and CRP were markedly elevated in non-survivors ($p < 0.001$). This is in agreement with **Yousaf *et al.*** [18] who linked high CRP, LDH, ferritin, and D-dimer to increased COVID-19 mortality and **Kapoor *et al.*** [19] who associated D-dimer elevation with severe disease, inpatient death, and thromboembolic events.

Also, **Kapoor *et al.*** [19] study showed that higher DIC scores and D-dimer levels are associated with severe COVID-19 illness, inpatient mortality, and pulmonary embolism risk.

The most reliable biomarkers for predicting severe outcomes in COVID-19 patients were found to be D-dimer and CRP. D-dimer had perfect diagnostic accuracy (AUC = 1.000), 100% specificity, and 97% sensitivity, while CRP performed similarly well (AUC = 0.985, 100% specificity, and 95% sensitivity). Additionally, serum ferritin demonstrated a strong prognostic value (AUC = 0.900), surpassing hemoglobin and lymphocyte count, which demonstrated only moderate predictive accuracy.

Ventilator-associated pneumonia is a serious lung complication that frequently affects severely ill COVID-19 patients undergoing invasive mechanical ventilation. COVID-19 individuals are about four times more likely to develop ventilator-associated pneumonia than those who do not have COVID-19[20].

EASIX scores were significantly higher among non-survivors, supporting its role as a prognostic tool. Several studies **Maes *et al.***[20], **Luft *et al.*** [21], **Pérez-García *et al.***[22] and **Gokcinar *et al.***[23] have demonstrated that high EASIX values predict poor outcomes in COVID-19 patients, including increased ICU mortality. According to a systematic review of 69 studies, the overall case fatality rate (CFR) for invasive mechanical ventilation (IMV) in critically-ill patients was 45% (95% CI: 39–52%) for 57,420 adult COVID-19 patients[24]. Our findings align with these reports, suggesting a robust link between elevated EASIX and higher mortality risk.

LIMITATIONS

The study's limitations include its retrospective single-center design, relatively small cohort, and a patient population skewed toward severe cases, which could overestimate mortality rates. Laboratory data were collected only at admission, which may not reflect dynamic changes during hospitalization.

CONCLUSION

In this study, advanced age, high ferritin, D-dimer, CRP, and elevated EASIX scores were significantly associated with mortality in COVID-19 patients. The EASIX index emerged as a simple and reliable predictor for early mortality risk assessment.

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