Original Article

trd Tuberculosis & Respiratory Diseases

Association between Age-Adjusted Endothelial Activation and Stress Index and Intensive Care Unit Mortality in Patients with Severe COVID-19

https://doi.org/10.4046/trd.2024.0081
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2024;87:524-531

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Received May. 31, 2024
Revised Jun. 27, 2024
Accepted Jul. 21, 2024
Published online Jul. 24, 2024

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Abstract

Background: Endothelial activation and stress index (EASIX) reflects endothelial dysfunction or damage. Because endothelial dysfunction is one of the key mechanisms, a few studies have shown the clinical usefulness of original and age-adjusted EASIX (age-EASIX) in patients with coronavirus disease 2019 (COVID-19). We aimed to evaluate the clinical utility of age-EASIX in predicting intensive care unit (ICU) mortality in critically ill patients with COVID-19 in South Korea.

Methods: Secondary analysis was performed using clinical data retrospectively collected from 22 nationwide hospitals in South Korea between January 1, 2020, and August 31, 2021. Patients were at least 19 years old and admitted to the ICU for severe COVID-19, demanding at least high-flow nasal cannula oxygen therapy. EASIX [lactate dehydrogenase (U/L)×creatinine (mg/dL)/platelet count (10^9 cells/L)] and age-EASIX (EASIX×age) were calculated and $\log_2$-transformed.

Results: The mean age of 908 critically ill patients with COVID-19 was 67.4 years with 59.7% male sex. The mean $\log_2$ age-EASIX was 7.38±1.45. Non-survivors (n=222, 24.4%) in the ICU had a significantly higher $\log_2$ age-EASIX than of survivors (8.2±1.52 vs. 7.1±1.32, p<0.001). Log_2 age-EASIX was significantly associated with ICU mortality (odds ratio, 1.541; 95% confidence interval, 1.322 to 1.796; p<0.001) and had a better area under the receiver operating characteristic curve than of the sequential organ failure assessment (SOFA) score in predicting ICU mortality (0.730 vs. 0.660, p=0.001).

Conclusion: Age-EASIX is significantly associated with ICU mortality and has better discriminatory ability than the SOFA score in predicting ICU mortality.

Keywords: COVID-19; Age; Endothelial Activation and Stress Index; Intensive Care Unit; Mortality

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has imposed a huge health burden worldwide and continues with the emergence of new variants[1-5]. The clinical spectrum of respiratory illness in COVID-19 ranges from a mild upper respiratory infection to a critically ill condition like severe pneumonia[6,7]. Critically ill patients with severe COVID-19 pneumonia admitted to the intensive care unit (ICU) have high multiorgan dysfunction and worse outcomes, including high mortality, despite intensive care[8-12]. Multiple and complex mechanisms have been involved in causing critically ill conditions after the SARS-CoV-2 infection[13,14]. Among them, vascular endothelial dysfunction caused by the viral infection itself or an immune reaction has been associated with a severe course and complications due to COVID-19[15-22]. Therefore, developing or repurposing an index to assess endothelial dysfunction in clinical practice is essential to predicting clinical course and determining the appropriate management in critically ill patients with COVID-19.

Endothelial activation and stress index (EASIX) was developed to evaluate endothelial dysfunction and predict mortality in patients with acute graft versus host disease (GVHD) after allogenic stem cell transplantation, and EASIX was significantly associated with high mortality[23-26]. EASIX has demonstrated clinical utility in other hematologic diseases[27,28], including sepsis prediction and outcome in allogenic stem cell transplantation[29,30]. Several studies reported that EASIX was also associated with the severity and outcome of COVID-19[31,32]. Regarding old age as not only an associated risk factor for endothelial dysfunction[33,34] but also a major determinant for worse outcome in COVID-19[8-11], age-adjusted EASIX (age-EASIX) also developed and was associated with death within 28 days in hospitalized patients[35]. However, the validation of the clinical utility of age-EASIX for ICU outcomes remains to be fully elucidated in critically ill patients with COVID-19.

This study aimed to evaluate the clinical utility of age-EASIX in predicting ICU mortality in critically ill patients with COVID-19 admitted to the ICU in South Korea.

Materials and Methods

1. Patients

We performed a secondary analysis of the clinical data of patients with COVID-19 from a nationwide, multicenter, retrospective cohort collected from 22 tertiary- or university-affiliated hospitals between January 1, 2020, and August 31, 2021. The patient was at least 19 years old, and the polymerase chain reaction test for COVID-19 was positive. The analysis included critically ill patients in the ICU requiring high-flow oxygen therapy.

This study was approved by the Institutional Review Board (IRB) of the Gyeong Sang National University Hospital (IRB number 2021-012-020) and the local committees of all other participating centers. Informed consent was waived due to the retrospective nature of the study.

2. Data collection and calculation of EASIX and age-adjusted EASIX

Baseline characteristics such as age, sex, body mass index, comorbidities, clinical frailty scale, sequential organ failure assessment (SOFA), clinical features, and laboratory and ventilatory parameters were collected. Clinical outcomes, such as ICU duration and mortality, were also collected.

3. Calculation of EASIX and age-EASIX

EASIX was calculated with the below equation originally suggested by Luft et al.[23] "EASIX= lactate dehydrogenase (LDH; U/L)×creatinine (mg/dL)/platelet count (10^9 cells/L)."

Age-EASIX was calculated with the following formula suggested by Perez-Garcia et al.[35] "age-EASIX=age (years)×LDH (U/L)×creatinine (mg/dL)/platelet count (10^9 cells/L)."

Both values were $\log_2$-transformed for analysis.

4. Statistical analysis

Non-continuous variables were expressed as numbers (%) and compared using the chi-square test or Fisher's exact test, whereas continuous variables were expressed as mean±standard deviation and compared using the Student's t-test or Mann–Whitney U test. Univariate and multivariate logistic regression analyses were performed to identify the factors associated with ICU mortality and to clarify whether age-EASIX was significant. A cut-off value to distinguish between low and high age-EASIX values was defined according to their sensitivity and specificity using a receiver operating characteristic (ROC) curve and the Youden method[36]. The Kaplan–Meier method and log-rank test were used to compare the ICU mortality between the low and high age-EASIX groups. All data were analyzed using the SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA) and MedCalc for Windows version 15.22.4 (Med-

Calc Software, Ostend, Belgium). The statistical significance was set at $p<0.05$.

Results

1. Baseline characteristics of patients

During the study period, a total of 1,114 patients with COVID-19 who received at least high-flow oxygen therapy were enrolled. Among them, 908 patients were eligible for EASIX calculation, and their clinical data were analyzed. During the ICU stay (mean 21.8±23.2 days), 222 patients (24.4%) died. The baseline characteristics are presented in Table 1. Non-survivors were significantly older and had more comorbidities, including hypertension, diabetes mellitus, chronic lung disease, cardiovascular disease, chronic kidney and neurological disease, and solid tumors, than non-survivors. Non-survivors had a significantly higher SOFA score than in survivors. Regarding treatment, the survivors received significantly more remdesivir, while other medications did not differ. Non-survivors received more renal replacement therapy and mechanical ventilation. Extracorporeal membrane oxygen was used more often as rescue therapy in survivors.

2. Comparison of laboratory parameters and log_2 EASIX and log_2 age-EASIX values

Table 2 compares laboratory parameters, log_2 EASIX, and log_2 age-EASIX. Platelet count was significantly lower in non-survivors, and conversely, creatinine

Table 1. Comparison of baseline characteristics of intensive care unit survivors and non-survivors

Variable	Total	Survivors	Non-survivors	p-value
Number	908	686	222	
Age, yr-old	67.4±13.9	65.5±13.8	73.5±12.6	<0.001
Male sex	542 (59.7)	413 (60.2)	129 (58.1)	0.580
BMI, kg/m^2	24.8±4.2	24.8±4.2	24.8±4.2	0.991
Comorbidities	670 (73.8)	483 (70.4)	187 (84.2)	<0.001
Hypertension	481 (53)	346 (50.4)	135 (60.8)	0.007
Diabetes mellitus	313 (34.5)	224 (32.7)	89 (40.1)	0.043
Chronic lung disease	70 (7.7)	45 (6.6)	25 (11.3)	0.022
Chronic liver disease	29 (3.2)	22 (3.2)	7 (3.2)	0.968
Cardiovascular disease	115 (12.7)	78 (11.4)	37 (16.7)	0.039
Chronic kidney disease	66 (7.3)	40 (5.8)	26 (11.7)	0.003
Chronic neurologic disease	131 (14.4)	84 (12.2)	47 (21.2)	0.001
Connective tissue disease	16 (1.8)	15 (2.2)	1 (0.5)	0.138
Hematologic malignancy	13 (1.4)	11 (1.6)	2 (0.9)	0.745
Solid tumor	60 (6.6)	34 (5)	26 (11.7)	<0.001
CFS	3.2±1.8	3±1.7	3.6±1.9	<0.001
SOFA score	4.4±3.02	3.9±2.7	5.7±3.6	<0.001
Use of remdesivir	678 (74.7)	527 (76.8)	151 (68.0)	0.009
Corticosteroid	872 (96.0)	659 (96.1)	213 (95.9)	0.937
Tocilizumab	88 (9.7)	71 (10.4)	17 (7.7)	0.236
RRT	109 (12.0)	31 (4.5)	78 (35.1)	<0.001
Use of HFNO	746 (82.2)	588 (85.7)	158 (71.2)	<0.001
Use of MV	537 (59.1)	339 (49.4)	198 (89.2)	<0.001
Prone position	191 (21.0)	130 (19.0)	61 (27.5)	0.007
ECMO	106 (11.7)	63 (28.4)	44 (6.4)	<0.001

Values are presented as mean±standard deviation or number (%).
BMI: body mass index; CFS: clinical frailty score; SOFA: sequential organ failure assessment; RRT: renal replacement therapy; HFNO: high flow nasal oxygen therapy; MV: mechanical ventilation; ECMO: extracorporeal membrane oxygenation.

Table 2. Comparison of laboratory parameters and value of EASIX and age-EASIX

Variable	Total	Survivors	Non-survivors	p-value
Number	908	686	222	
WBC, $\times10^3/mm^3$	8.9±6.8	8.4±4.7	10.4±10.8	0.009
Hb, g/dL	13±2.1	13.2±2	12.5±2.1	<0.001
Platelet, $\times10^3/mm^3$	194.6±79.4	200.7±80	175.6±74.6	<0.001
BUN, mg/dL	23.5±16.5	20.1±13.9	30.6±21	<0.001
Creatinine, mg/dL	1.1±1.3	1±1.1	1.5±1.6	<0.001
Albumin, g/dL	3.3±0.5	3.3±0.5	3.1±0.5	<0.001
LDH, U/L	598.8±713.2	536.4±316.3	791.9±1,315.9	<0.001
CRP, mg/dL	25.3±73.8	23.4±51.6	30.8±118.5	0.013
D-dimer	3.6±7.7	3.2±6.8	5.0±9.8	<0.001
PaO_2/FiO_2 ratio, mm Hg	164.2±99.7	172.9±102.6	139.4±86.6	<0.001
Log_2 EASIX	1.34±1.34	1.11±1.21	2.05±1.47	<0.001
Log_2 age-EASIX	7.38±1.45	7.1±1.32	8.2±1.52	<0.001

Values are presented as mean±standard deviation.
EASIX: endothelial activation and stress index; WBC: white blood cell; Hb: hemoglobin; BUN: blood urea nitrogen; LDH: lactate dehydrogenase; CRP: C-reactive protein; PaO_2/FiO_2: partial pressure of arterial oxygen/fraction of inspired oxygen.

Table 3. Univariate and multivariate analyses for factors associated with intensive care unit mortality

Variable	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Male sex	0.917	0.674–1.247	0.580			
BMI	0.995	0.959–1.032	0.800			
Comorbidities*	2.246	1.511–3.338	<0.001	1.551	1.021–2.357	0.040
CFS	1.184	1.092–1.284	<0.001			
SOFA	1.188	1.133–1.246	<0.001	1.069	1.009–1.133	0.023
Log_2 age-EASIX	1.735	1.541–1.952	<0.001	1.564	1.367–1.789	<0.001

*Comorbidities include hypertension, diabetes mellitus, chronic lung disease, cardiovascular disease, chronic neurologic disease, chronic kidney disease, chronic liver disease, connective tissue disease, solid tumor and hematologic malignancy.
OR: odds ratio; CI: confidence interval; BMI: body mass index; CFS: clinical frailty score; SOFA: sequential organ failure assessment; EASIX: endothelial activation and stress index.

and LDH were significantly higher in non-survivors than those of survivors. The mean log_2 EASIX and log_2 age-EASIX values were 1.34±1.34 and 7.38±1.45, respectively. Non-survivors had significantly higher log_2 EASIX and log_2 age-EASIX than those of survivors (log_2 EASIX, 2.05±1.47 vs. 1.11±1.21, p<0.001; and log_2 age-EASIX, 8.2±1.52 vs. 7.1±1.32, p<0.001).

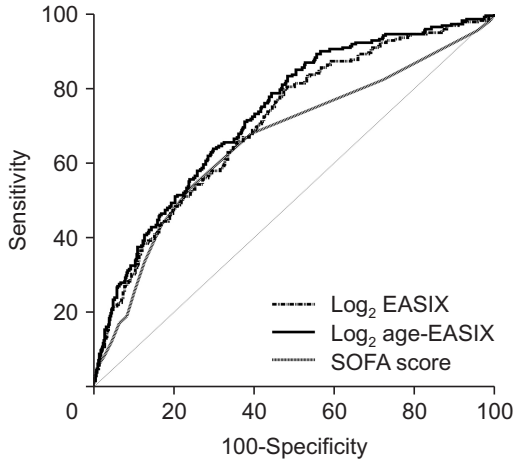
3. Factors associated with ICU mortality

Table 3 shows univariate and multivariate logistic regression analyses performed to evaluate associated factors in ICU mortality. The presence of comorbidities (odds ratio [OR], 1.551; 95% confidence interval [CI], 1.021 to 2.357; p=0.040), SOFA score (OR, 1.069; 95% CI, 1.009 to 1.133; p=0.023), and log_2 age-EASIX (OR, 1.564; 95% CI, 1.367 to 1.789; p<0.001) were significantly associated with the ICU mortality.

4. Comparison of ROCs between SOFA, log_2 EASIX, and log_2 age-EASIX

ROC curve analysis was conducted to compare the log_2 EASIX, SOFA score, and log_2 age-EASIX for predicting ICU mortality (Figure 1). The area under the ROC curve (AUROC) of log_2 age-EASIX to discriminate ICU

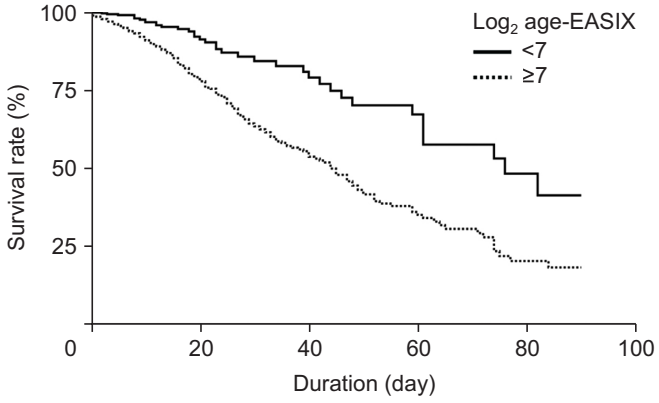
Figure 1. Comparison of receiver operating characteristic curve. *p<0.001. †p=0.0411. ‡p=0.0016. EASIX: endothelial activation and stress index; SOFA: sequential organ failure assessment; AUROC: area under the receiver operating characteristic curve; CI: confidence interval.



Variables	AUROC	95% CI
Log_2 EASIX*, †	0.706	0.675–0.736
Log_2 age-EASIX*, ‡	0.730	0.700–0.759
SOFA score†, ‡	0.660	0.629–0.691

mortality was 0.730 (95% CI, 0.700 to 0.759; p<0.001), with 83.3% sensitivity and 51.3% specificity. The AUROCs for SOFA and log_2 EASIX were 0.660 (95% CI, 0.629 to 0.691; p<0.001) and 0.706 (95% CI, 0.675 to 0.736; p<0.001), respectively. AUROC of log_2 age-EASIX was significantly higher than that of both SOFA and log_2 EASIX for predicting ICU mortality (log_2 age-EASIX vs. SOFA score, p=0.0016; and log_2 age-EASIX vs. log_2 EASIX, p<0.001). We divided the patients into two groups using a 7.00 cut-off value of log_2 age-EASIX. The Kaplan-Meier survival curve showed that patients with a log_2 age-EASIX ≥7 had a lower survival rate than patients with a log_2 age-EASIX <7.00 (p<0.001) (Figure 2).

Figure 2. Kaplan Meier survival curve according to log_2 age-endothelial activation and stress index (EASIX).



Discussion

Our study showed that age-EASIX was significantly associated with ICU mortality in critically ill patients with COVID-19 admitted to the ICU requiring at least high-flow oxygen therapy, and its discrimination performance in predicting ICU mortality was better than that of the EASIX and SOFA scores in South Korea.

The COVID-19 pandemic has caused a huge health burden worldwide[3,4]. Critically ill patients with COVID-19, such as those with a high oxygen demand, had high mortality rates[8-12]. The pathogenesis of COVID-19 following SARS-CoV-2 invasion into the respiratory tract has been recognized as a multiple and complex process that has played a role in multiple organ dysfunction[13,14]. Vascular endothelial inflammation and dysfunction have been observed in the SARS-CoV-2 infection[15-17,19,37]. SARS-CoV-2 infection-associated endothelial dysfunction has been reported as an important mechanism resulting in multiple organ damage in patients with COVID-19[18,20-22,38-40]. Therefore, developing or repurposing an index to assess endothelial dysfunction or damage in clinical practice is crucial to predicting clinical course and determining or moving forward with appropriate management in critically ill patients with COVID-19.

EASIX, which was initially described by Luft et al.[23,24,26] and calculated using LDH, creatinine, and platelet levels developed for the purpose of assessing endothelial dysfunction in patients with allogeneic stem cell transplantation and acute GVHD after allogeneic stem cell transplantation, was significantly associated with high mortality. EASIX has also been shown to be clinical useful to evaluate prognosis in other hematologic diseases and sepsis prediction and outcome in allogeneic stem cell transplantation[27-29].

Several studies have been conducted on EASIX in patients with COVID-19[31,32]. Kalicinska et al.[31], for the first time, reported a retrospective analysis of the association between the EASIX score and clinical outcomes in 523 hospitalized patients with COVID-19, with or without coexisting hematological cancer. Their study revealed that EASIX was a strong predictor of ICU admission, in-hospital mortality, and the occurrence of acute renal failure in both hematological and non-he-

matological patients with COVID-19[31]. Zinczuk et al.[32], in their retrospective analysis of the medical data of 370 hospitalized patients with severe COVID-19, reported that non-survivors had a significantly higher $\log_2$ EASIX value than survivors (6.66 vs. 2.94, p<0.0010). They showed that the AUC for predicting mortality in patients with COVID-19 was 0.646 (95% CI, 0.589 to 0.702)[32].

Old age has been consistently reported as a significant risk factor associated with high mortality in critically ill patients with COVID-19[8-11]. Aging is also known to be an associated factor for endothelial dysfunction, which reflects high cardiovascular complications in the general population[33,34]. Considering the importance of age in patients with COVID-19, Perez-Garcia et al.[35] adjusted EASIX to age (EASIX multiple by age) and transformed $\log_2$ for analysis. In their retrospective study involving patients with COVID-19 from derivation (n=1,200 patients) and validation cohorts (n=1,830 patients), both $\log_2$-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 good predictive performance for 28-day mortality both in the derivation cohort (AUROC=0.827) and validation cohort (AUROC=0.820), with better predictive performance for 28-day mortality than $\log_2$-EASIX (p<0.001)[35]. This study suggests that age adjustment for EASIX is necessary to achieve good performance in predicting outcomes in COVID-19 patients. EASIX, or age-adjusted EASIX, has yet to be validated, and its clinical utility in critically ill patients with severe COVID-19 admitted to the ICU in South Korea remains to be elucidated. Our findings from a retrospective, nationwide, multicenter cohort study in South Korea were similar to those of previous studies. Our study found that age-EASIX in patients with COVID-19 was significantly higher in non-survivors than in survivors. In the multiple variable analysis, age-EASIX was associated with increased ICU mortality and performed better in predicting ICU mortality than EASIX and SOFA scores. The SOFA score has been widely used in intensive care settings to assess organ dysfunction and predict mortality in critically ill patients before COVID-19 pandemic[41]. Regarding, however, its role in predicting mortality in severe COVID-19 patients, it is not robustly established and remains inconclusive. While the SOFA score includes several indicators of organ failure, it does not account for age, which is a significant risk factor in severe COVID-19 cases. A couple of studies suggest that the SOFA score have the limit to predict mortality compared to age and raise a question about its utility compared to age[42,43]. The EASIX score, developed in the hematologic field, reflects endothelial dysfunction/damage, which is a key mechanism in COVID-19. It may provide earlier insights into endothelial dysfunction/damage compared to the SOFA score. Therefore, combining age with the EASIX score might have a potential to offer a more accurate of mortality in severe COVID-19 patients compared to relying solely on SOFA score.

Our study has several limitations. First, the clinical data of patients were collected retrospectively from a nationwide multicenter study in South Korea, and selection bias cannot be ruled out. Second, most of our patients were in the early pandemic period, and the clinical impact of age-EASIX on patients in the late variant pandemic in South Korea remains to be validated. Third, the age-EASIX was only assessed at admission, and the clinical impact of serial age-EASIX values on patient outcomes remains to be determined. Fourth, age-EASIX did not compare other scores such as quick Sequential Organ Failure Assessment (qSOFA), National Early Warning Score (NEWS), or Systemic Inflammatory Response Syndrome (SIRS) due to lack of clinical data.

In conclusion, our study suggests that age-adjusted EASIX is a feasible index to predict ICU mortality in critically ill patients with COVID-19 admitted to the ICU requiring high-dose oxygen therapy. Additionally, age-adjusted EASIX may outperform EASIX and SOFA scores in predicting ICU mortality.

Authors' Contributions

Conceptualization: Jeong JH, Heo M, Yoo JW. Methodology: Jeong JH, Heo M, Yoo JW. Formal analysis: Jeong JH, M Heo, Yoo JW. Data curation: Park S, Lee SH, Park O, Kim T, Yeo HJ, Jang JH, Cho WH, Yoo JW. Validation: Park S, Lee SH, Kim T, Yeo HJ, Jang JH, Cho WH, Yoo JW. Investigation: Park S, Lee SH, Kim T, Yeo HJ, Jang JH, Cho WH, Yoo JW. Writing - original draft preparation: Jeong JH, M Heo, Yoo JW. Writing - review and editing: Yoo JW. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Funding

No funding to declare.

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