Endothelail and Stress Index as One of New Prognostic Determinants of COVID- 19 Severity

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Receive date:27/4/2023
Revise date:11/5/2023
Accept date:23/5/2023
Publish date:1/6/2023
Key words:
COVID-19; EASIX; D-Dimer; ferritin; Lymphocyte/Monocyte ratio.

Background and study aim: COVID-19 pandemic began in China in 2019. The disease course can be unnoticed, mild, aggressive or end by death. Several prognostic markers have been studied in order to minimize the severity of the disease or its danger. This study aims at investigating the prognostic value of Endothelial activation and stress index (EASIX) as a new predictor in addition to some haematological, biochemical, computerized tomography (CT), electrocardiogram (ECG) and echocardiography (Echo) findings as determinants of the COVID-19 severity.

Patients and Methods: 105 non-vaccinated COVID-19 patients aged 17–89 admitted to a referral hospital in Alexandria, Egypt, from January to August 2022 with positive nasopharyngeal qualitative PCR swabs were included. Considerations include demographics, history, hospital stay, and intensive care unit (ICU) admission. Complete blood picture with differential count, C-reactive protein, ferritin, D-Dimer, liver and renal function tests, lactate dehydrogenase, cardiac markers, EASIX, chest CT, ECG, and Echo were done.

Results: EASIX along with D-Dimer and ferritin showed statistically significant sensitivity and specificity when analysed as predictors for COVID-19 mortality, need for ICU admission and mechanical ventilation, while lymphocyte/monocyte ratio (LMR) showed statistically significant sensitivity and specificity only for COVID-19 mortality and need for ICU admission. D-Dimer had the highest overall accuracy, followed by ferritin, EASIX, and the lowest accuracy appear in LMR.

Conclusion : Because of its strong correlation with COVID-19 mortality, ESAIX should be added as a new biomarker to the existing set of biomarkers linked to poor prognosis namely D-Dimer and ferritin .

INTRODUCTION

COVID-19 or severe acute respiratory syndrome (SARS-COV.2) is a worldwide pandemic **[1]**. It was found that COVID-19 binds to angiotensin converting enzyme 2 receptor (ACE2) causing endotheliopathy which activates the coagulation system resulting in thrombosis as well as complement activation **[2]**. This receptor is widely distributed all over the body namely smooth muscle, lung alveolar cells, enterocytes, venous and arterial endothelium and brain stem **[3]**. One of the characteristics of COVID-19 is a substantial depletion of host immune cells as well as immune over activation causing massive immune injury with lymphocyte damage. Different presentations have been found for this disease namely fever, headache, generalized body ache. fatigue, anosmia & dyspnoea **[4]**. The diagnosis of COVID-19, in terms of positive or negative test, is primarily based on laboratory tests, chest imaging modalities, including chest X-ray (CXR) & computed tomography (CT) **[5]**.

Previous studies had indicated that respiratory system was the notably affected one **[6,7]**, but other post mortem analysis had stated that cardiac **[8,9]**, renal [**10]** hepatic & hematopoietic system **[9,11]** were also affected as well and to a varying degree that increased with the severity of the patients' preexisting comorbidities.

New discoveries of the disease biology have been introduced which made the outcome of its management differ from patient to patient. This is due to heterogeneity of the clinical course which represents a challenge to the clinicians as about 80% of COVID-19 patients are not hospitalized due to mild disease **[12]**. As the pandemic enters its third year, various treatment protocols have been created in the hopes of eradicating the disease. Early detection of disease severity by finding appropriate prognostic determinant could be lifesaving; hence we aimed at investigating the prognostic value of EASIX in addition to some haematological, biochemical, CT and ECG findings as determinants of the COVID-19 severity**.**

PATIENTS AND METHODS

Study design and patients: One hundred & five COVID-19 patients aged between 17 to 89 years with positive nasopharyngeal qualitative PCR swabs were included in this study. All patients were not vaccinated. Patients with chronic lung or cardiovascular disease, autoimmune disorders or cancer were excluded. This study was carried out in a COVID-19 referral hospital in Alexandria, Egypt, from January to August 2022. Patients' demographic data including age and gender was taken at the time of diagnosis.

Blood Sample collection and processing: 7 ml of blood samples were collected from each patient; 2 mL were placed in VACUETTE® EDTA tube for complete blood picture assessment with automated differential count which was performed on an ADVIA® 2120i Hematology Analyzer (Siemens), and microscopic examination was done for differential count confirmation. The second 2mL were placed in VACUETTE® citrated plasma tube for D-Dimer assessment through latex test using biolab diagnostic kits with reference value (R.V) of less than 250 ng/mL using Cobas -C Roche®. The remaining 3 mL were placed in VACUETTE® Z serum sep clot activator tube and centrifuged at 2000 g for 10 min at room temperature to assess biochemical parameters using HITACHI AUTOMATIC ANALYZER COBAS 6000, lot (52520500), the parameters included C-reactive protein (CRP), ferritin, liver function tests (alanine transaminase (ALT) and aspartate transaminase (AST), renal function tests (urea and creatinine), lactate dehydrogenase (LDH), and cardiac markers (troponin-I). All tubes were from Greiner Bio-one International GmbH.

R.V. of CRP by quantitative nephelometric is less than 3 mg/L, ferritin R.V. is 30–400 ng/ml for males and 15–150 ng/mL for females. R.V. for AST is 40 U/L and for ALT is up to 41 U/L. Urea R.V is 10 – 50 mg/dL and for creatinine is 0.7 - 1.2 mg/dL for male and 0.5 - 0.9 mg/dL for female. For LDH R.V is 230 - 460 U/L, and for troponin-I is up to 0.3 ng/ml.

Endothelial activation and stress index (EASIX) were calculated according to the formula: LDH [u/l] x creatinine [mg/dL]/thrombocytes [$10^{\wedge 9}$ cells/L] **[13]**.

Radiological findings including cardiac assessment by using Echocardiogram (ECG) to assess heart rate, rhythm and predict signs of ischemia. Transthoracic echocardiography (Echo) for assessment of chamber sizes, valvular conditions, systolic and diastolic functions and wall motion abnormalities was used.

High-resolution computerized topography (HRCT) scans of the chest were performed for all patients using multi-detector CT scanner (GE Bright®, speed 8 detector) on admission. The patients were placed in supine position with the head advanced and breathing held for scanning. The scan level was from the chest entrance to the bottom of the lungs.

The scanning parameters were as follows: thickness of the slices = 5 mm, interslice gap = 5 mm, matrix = 512 mm× 512 mm, tube voltage = 120 kV, current = 250-300 mA, collimation of 10 mm, and pitch of 1:1.675. No contrast was administered. The post-processing workstation reconstructed all images using high-resolution and conventional algorithms with lung window of +1600 to 600 HUs and mediastinal window of 40 to 350 HUs.

Image analysis

The HRCT images were evaluated for the following characteristics: (1) 4 types of lesion distributions, the side distribution; unilateral or

bilateral, the transverse distribution; central and peripheral, the cranio-caudal distribution; upper lung predominant, lower lung predominant, and the scattering distribution, 1, 2 and ≥ 3 lesions; (2) lesion morphology: ground-glass opacities (GGO), consolidation, mixed GGO and consolidation; (3) pleural effusion.

The clinical data and disease course, including recovery, intensive care unit (ICU) admission, and mechanical ventilation, were inspected. The study's outcome was either recovery or death.

Statistical analysis

Data were entered, verified and analysed using SPSS v.25.0 for Windows (SPSS, Inc., Chicago, IL, USA). Categorical variables were presented as frequencies and percentages, and continuous variables were presented as mean and standard error (S.E). Independent-samples t test and Chi square test were used for mean comparison between studied groups. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated. Area under the receiver operating characteristic (ROC) curve was used for testing sensitivity and specificity of studied variables. Pearson correlation was used to test correlation among the different studied parameters. Statistical significance was assumed at a level of p values < 0.05.

Consent to participate. The manuscript has been read and approved by all authors.

RESULTS:

1- Demographic data and clinical findings among patients

105 COVID-19 patients were enrolled in this study including 68 males and 37 females (65%, 35%; respectively) with mean age (54 ± 1.5) and range (17-89 years old). Patients showed variable symptoms including fever, cough, fatigue, chest pain, dyspnea, headache and gastrointestinal manifestations (65%,72%,68%,38%, 49%,2%, and 17%; respectively). Taste and smell were lost in 41% of patients. 1% lost taste only while 3 % lost smell only. (Table 1).

2- Treatment protocol and hospitalization fate in patients

Among our patients, 48% were home isolated, while the remaining 52% were hospitalised. From 105 patients, 3 (2.9%) received no treatment, 51 (48.6%) patients received home treatment protocol, and 51 (48.6%) had hospital treatment protocol. 73% of patients were recovered and 27% died.

From the recovered patients 65% were home isolated; while 35% were hospitalized, 14% of them were ICU admitted and 5 % were mechanically ventilated. All died patients were hospitalized 100%; 89% of them were ICU admitted and 79 % were mechanically ventilated. (Table 2).

3- Laboratory findings among COVID-19 patients

3.1 Complete blood picture findings

Some CBC parameters showed statistically significant decrease between dead and recovered patients as regards haemoglobin (Hb), haematocrit (HCT), mean corpuscular volume (MCV), and mean corpuscular haemoglobin (MCH) (p= 0.001, 0.038, 0.019, and 0.004 respectively), while statistically significant increase was shown in LMR (p= 0.044) (Table 3).

3.2 Biochemical and endothelial markers

When comparing dead patients to those who recovered, there was a statistically significant increase in biochemical markers including; D-Dimer, CRP, ferritin, LDH, Troponin, ALT, AST, ALT/AST ratio, urea, and creatinine. (Table 4).

The endothelial activation and stress index marker (EASIX) showed a highly statistically significant increase in dead patients compared to recovered one (*p*=0.00) (Table 4).

4- Sensitivity, specificity and AUC for predicting hospitalization fate

4.1 Sensitivity, specificity and AUC For predicting mortality in COVID 19 patients

D-Dimer (ng/ml), ferritin (µg/L), EASIX, and lymphocyte/monocyte ratio (LMR) were analysed as predictors for **COVID-19 mortality**. The four parameters showed statistically significant sensitivity and specificity (*p*= 0.00,0.00,0.00, and 0.044; respectively). D-Dimer had the highest accuracy of 86% (AUC=0.86) followed by ferritin 77.2% (AUC=0.772), EASIX 72.8% (AUC=0.728), and the least one was for LMR with the value of 61.5% (AUC=0.615). Table 5, Figure 1

4.2 Sensitivity, specificity and AUC For predicting ICU admission in COVID 19 patients

By studying the same four parameters as regards **ICU admission** in COVID-19 patients we found that all of them had significant sensitivity and specificity (*p*=0.01,0.00,0.00, and 0.033; respectively). Table 6, Figure 2. D-Dimer had the highest overall accuracy of 74 (AUC= 0.744), followed by ferritin 72 % (AUC=0.719), EASIX 65% (AUC=0.653, and the lowest accuracy appear in LMR 60% (AUC=0.595).

4.3 Sensitivity, specificity and AUC For predicting mechanical ventilation in COVID 19 patients

When the previous four parameters were analysed by measuring their sensitivity and specificity as predictors for requirement of **mechanical ventilation** in our patients, we found that D-Dimer, ferritin, and EASIX were statically significant with p value of 0.005, 0.00, and 0.00; respectively with over all accuracy of 82 % for D-Dimer, 74 % for ferritin and 69% for EASIX; while LMR didn't show any statistically significant sensitivity nor specificity. (Table 7, Figure 3).

5- CT findings & Cardiac assessment tests

Table (8&9) showed the detailed analysis of chest CT imaging;39 patients (37.14%) were classified as early stage (Figure 4) from them 16 patients had ground glass opacity (GGO), 8 patients had patchy consolidation while 15 patients had mixed of GGO and consolidation. Progression stage were detected in 54 patients (Figure 5), from them 8 (14.81%) patients had GGO, 15 (27.77%) patients had patchy consolidation and 31 (57.40%) patients had mixed of GGO and consolidation. The last 12 (11.42%) patients were classified as advanced stage (Figure 6) from them 4 (33.33%) patients had patchy consolidation and 8 (66.66%) had mixed of GGO and consolidation.

Table 7 also showed that both Echo & ECG detect the same findings in which all recovered patients were free of any cardiac complications after infection while 11/28 of died patient (39.3%) expressed cardiac problems .

Table 1: Demographic data and clinical findings in 105 COVID-19 patients

Demographic and clinical findings		N	%
Gender	**Male**	68	65%
	Female	*37*	*35%*
Symptoms	***Fever***	*68*	*65%*
	Cough	*76*	*72 %*
	Fatigue	*70*	*68%*
	Chest pain	40	38%
	Dyspnea	51	49%
	Headache	2	2%
	gastrointestinal manifestations	18	17%
	Taste and smell loss	43	41 %
	Taste loss	1	1%
	Smell loss	3	3%

https://aeji.journals.ekb.eg/
DOI: 10.21608/AEJI.2023.206428.1287

Table 2: Treatment protocol & Hospitalization fate in 105 COVID-19 patients

		Recovered (n=77) N (%)	Death (n=28) N (%)	P	χ^2	O. R	C.I 95%
Hospitalization	**Home isolation**	50 64.9%	0 0%	0.000	34.71	0.351	0.259 – 0.475
	Hospitalized	27 35.1%	28 100%				
Treatment	**No treatment**	3 3.9%	0 0%	0.000	21.18	-	-
	Home protocol	47 61.0%	4 14.3%				
	Hospital protocol	27 35.1%	24 85.7%				
ICU	**No Admission**	66 85.7%	3 10.7%	0.000	51.26	50	2.7 – 23.4
	ICU Admission	11 14.3%	25 89.3%				
MV	**No Mechanical Ventilator**	73 94.8%	6 21.4%	0.000	59.34	66.92	17.3 – 258.6
	Mechanical Ventilator	4 5.2%	22 78.6%				

Table 3: Complete blood picture findings in 105 COVID-19 patients

	Recovered (n=77) Mean ± S. E	Death (n=28) Mean ± S. E	P
RBCs (UL*10^6)	4.82 ± 0.71	4.59 ± 0.13	0.106
Hb (g/dL)	*13.20 ±0.19*	*11.85 ±0.35**	0.001
HCT (%)	*38.84 ±0.74*	*35.98 ± 0.99**	0.038
MCV (fl)	*81.89 ± 0.67*	*78.55 ± 1.43**	0.019
MCH (pg)	*27.55 ± 0.28*	*25.86 ±0.56**	0.004
MCHC (g/dL)	33.42 ± 0.24	32.88± 0.23	0.206
RDW (%)	13.79 ± 0.21	14.33 ± 0.33	0.193
WBCs (UL*10^3)	7.01 ± 0.43	7.41 ± 0.78	0.642
Neutrophils (*10^3/ml)	4.93 ± 0.39	5.15 ± 0.66	0.772
Band (UL*10^3)	0.055 ± 0.02	0.14 ± 0.07	0.128
Lymphocytes (UL*10^3)	1.38 ± 0.08	1.55 ± 0.16	0.325
Monocytes (UL*10^3)	0.49 ± 0.03	0.48 ± 0.08	0.781
Eosinophils(*10^3/ml)	0.045 ± 0.01	0.046 ± 0.01	0.959
Basophils (*10^3/ml)	0.008 ± 0.003	0.004 ± 0.0036	-0.069
Platelets (*10^3/ml)	234.8 ± 10.19	275 ± 34.10	0.149
Lymphocyte / Monocyte ratio	*3.3 ± 0.22*	*4.27 ± 0.47**	0.197

Table 4. Biochemical and endothelial markers:

	Recovered (n=77) Mean ± S.E	Death (n=28) Mean ± S.E	P
D-Dimer (ng/mL)	190.81 ± 12.49	362.96 ± 31.52*	0.00
CRP (mg/L)	4.19 ± 0.58	13.35 ±01.89*	0.00
Ferritin (ng/mL)	278.72 ± 16.84	490.3 ± 45.92*	0.00
ALT (U/L)	33.32 ± 3.47	47.89 ± 7.19*	0.046
AST (U/L)	30.34 ± 3.75	51.89 ± 9.76*	0.013
AST/ALT ratio	0.92 ± 0.03	1.10 ± 0.10*	0.014
Urea (mg/dL)	36.34 ± 3.96	64.07 ± 9.95*	0.002
Creatinine(mg/dL)	1.00 ± 0.045	1.60 ± 0.21*	0.00
LDH (U/L)	356.91 ± 13.32	502.07 ± 32.14*	0.00
Troponin-I (ng/mL)	0.014 ± 0.0021	0.34 ± 0.15*	0.00
EASIX	1.78 ± 1.17	3.47 ± 0.45*	0.00

Table 5: Sensitivity, specificity and AUC for predicting mortality

	AUC	95% CI	P	Sensitivity	Specificity	Youden's index	Cut-off value
D-Dimer (ng/mL)	0.860	0.780 – 0.940	0.00	82	35	0.172	199
Ferritin (ng/mL)	0.772	0.663 – 0.881	0.00	85	43	0.286	279
EASIX	0.728	0.611 – 0.844	0.00	71	32	0.039	1.99
Lymphocyte / Monocyte ratio	0.615	0.492 – 0.737	*0.044*	*71*	50	0.221	2.82

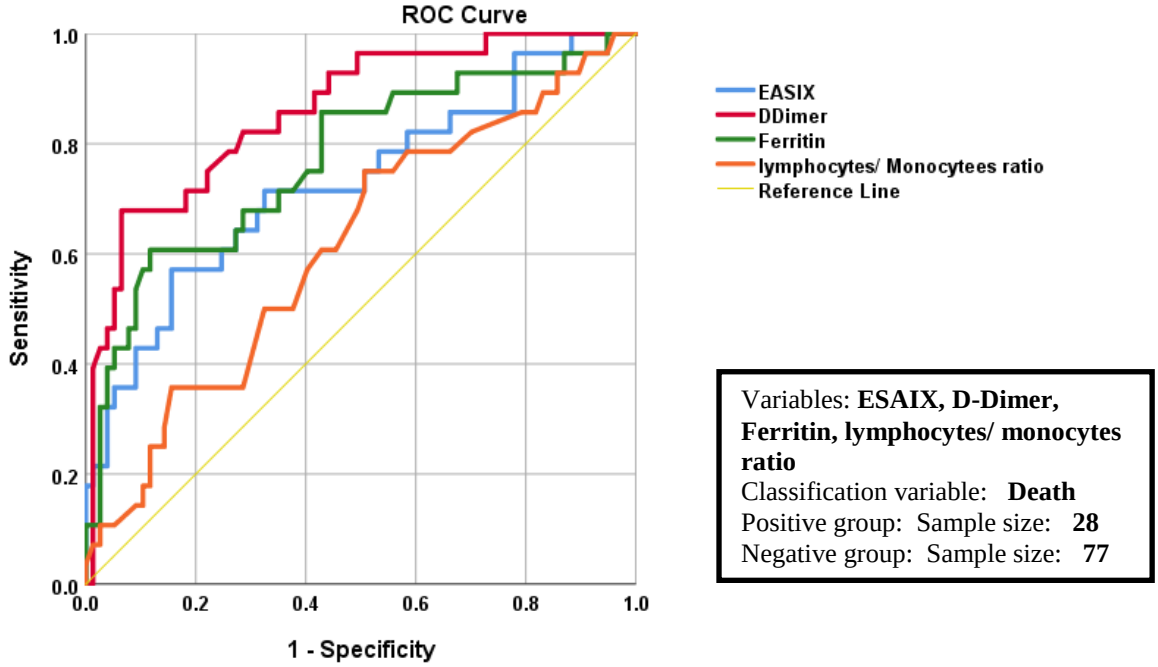

Figure 1: Area under the ROC curve of ESAIX, D-Dimer(ng/ml), Ferritin(µg/L), and lymphocytes/monocytes ratio as a discriminator for death. (n=105)

Table 6: Sensitivity, specificity and AUC for predicting ICU admission

	AUC	95% CI	P	Sensitivity	Specificity	Youden's index	Cutoff value
D-Dimer (ng/mL)	0.744	0.641 – 0.846	0.00	69.5	39	0.086	193.5
Ferritin (ng/mL)	0.719	0.61 – 0.828	0.00	78	49	0.271	263.5
EASIX	0.653	0.54 – 0.766	0.01	72	58	0.302	1.37
Lymphocyte / Monocyte ratio	0.595	0.480 – 0.711	*0.033*	*75*	58	0.33	2.45

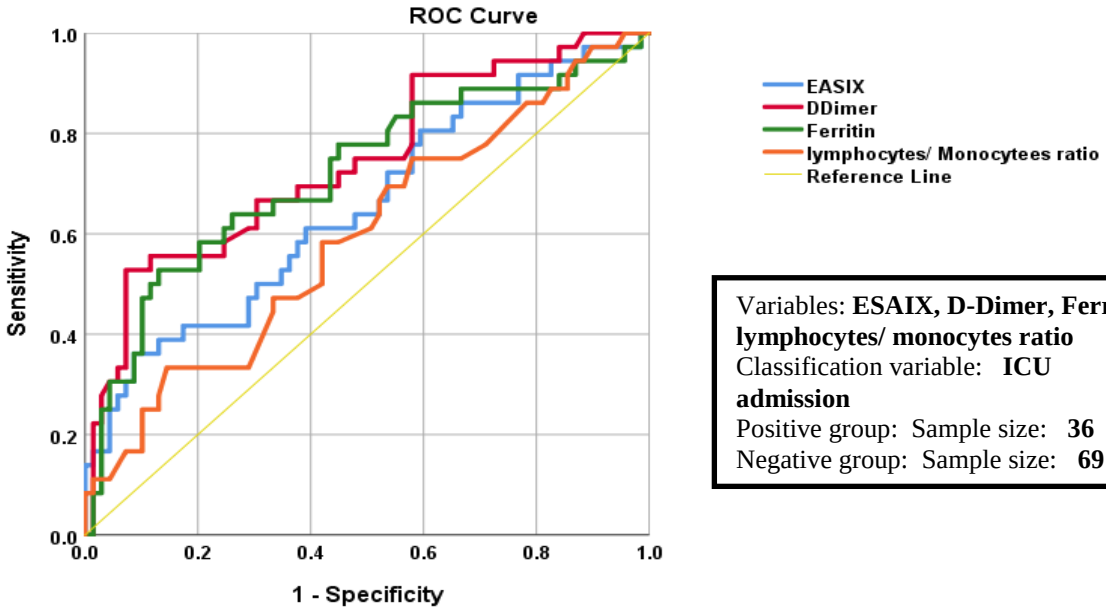

Figure 2: Area under the ROC curve of ESAIX, D-Dimer(ng/ml), Ferritin(µg/L), and lymphocytes/monocytes ratio as a discriminator for ICU admission. (n=105)

Table 7: Sensitivity, specificity and AUC for predicting mechanical ventilation

	AUC	95% CI	P	Sensitivity	Specificity	Youden's index	Cutoff value
D-Dimer (ng/mL)	0.823	0.731 – 0.915	0.00	85	37	0.213	196.5
Ferritin (ng/mL)	0.742	0.628 – 0.857	0.00	73	35	0.085	313.5
EASIX	0.685	0.551– 0.820	0.005	73	51	0.25	1.51
Lymphocyte / Monocyte ratio	0.564	0.435 – 0.693	0.18	*69*	58	0.275	2.55

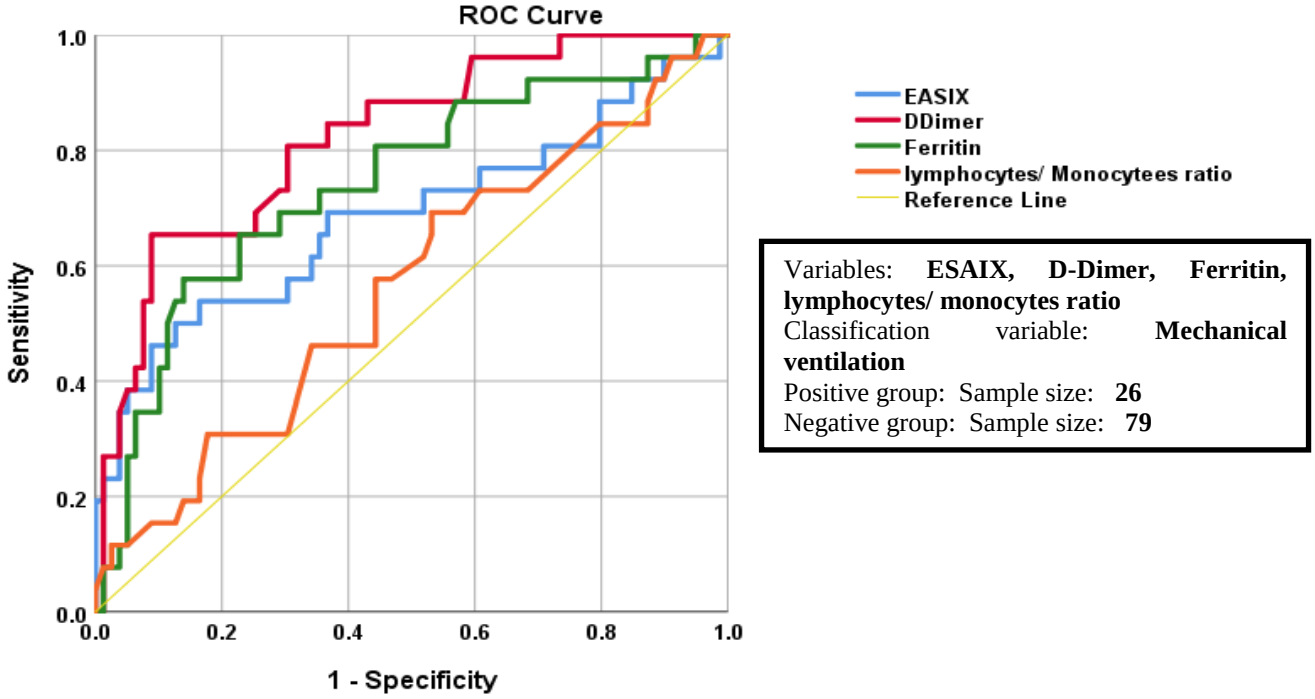

Figure 3: Area under the ROC curve of ESAIX, D-Dimer(ng/ml), Ferritin(µg/L), and lymphocytes/monocytes ratio as a discriminator for mechanical ventilation.(n=105

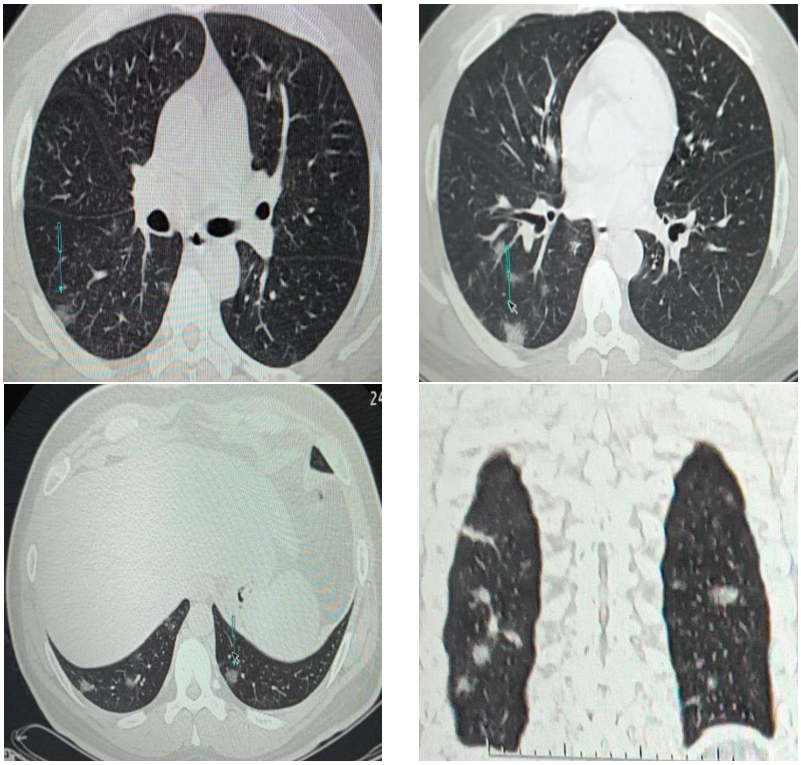

Figure 4: Early changes: A 43-year-old male COVID-19 patient. HRCT Chest image showed multiple small patchy areas of ground glass opacities are seen scattered in both lower lung lobes.

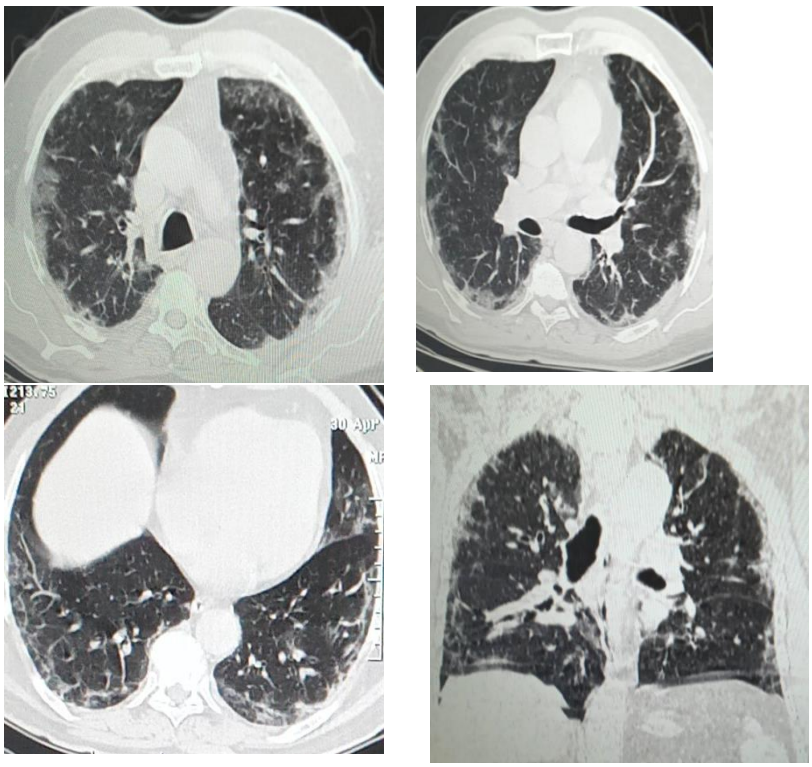

Figure 5: Progressive changes: A 65-year-old female COVID-19 patient. HRCT Chest image showed multiple small ill-defined patchy areas and veiling opacities of alveolar shadowing and consolidative pulmonary changes scattered in the peripheral aspect of both lung fields.

DOI: 10.21608/AEJI.2023.206428.1287

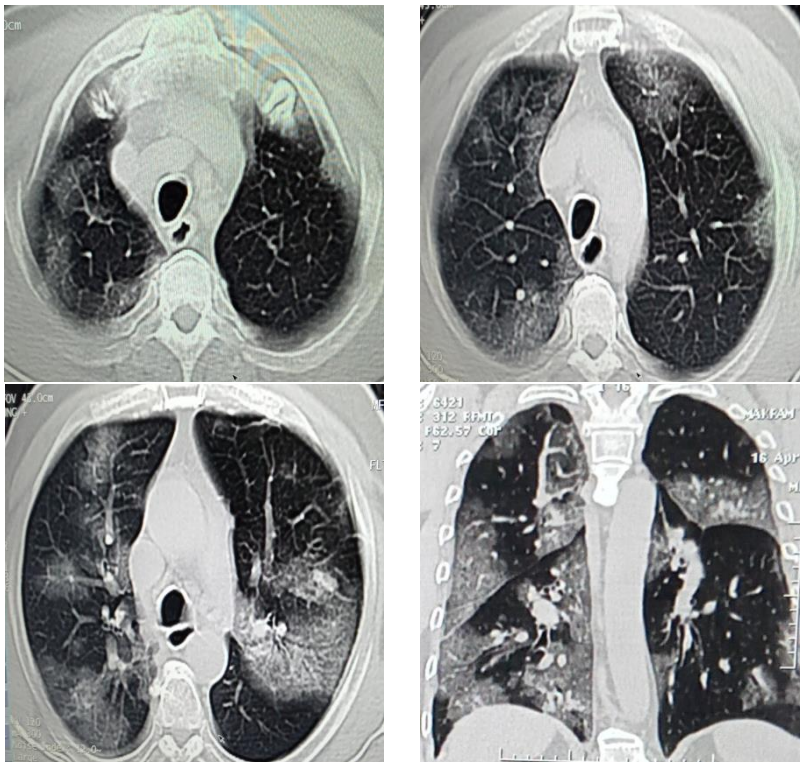

Figure 6: Advanced changes: A 52-year-old male COVID-19 patient. HRCT Chest image showed Extensive Multiple ground glass opacities infiltrating all lung lobes bilaterally.

Table 8: CT findings & Cardiac assessment tests

		Recovered (n=77) N (%)	Death (n=28) N (%)	P	χ^2	O. R	C.I 95%
CT staging	Early	31 40%	8 29%	0.53	1.27	–	–
	Progressive	38 49%	16 57%				
	Advanced	8 11%	4 14%				
ECG	Normal	77 100%	17 60.7%	0.00	33.79	1.647	1.223 – 2.219
	CAD	0 0%	11 39.3%				
Echo	Normal	77 100%	17 60.7%	0.00	33.79	1.647	1.223 – 2.219
	CAD	0 0%	11 39.3%				

Table 9: Chest CT findings of 105 patients with COVID-19 pneumonia

Imaging presentation	Imaging stage		
	Early (n=39) N (%)	Progression (n=54) N (%)	Advanced (n=12) N (%)
GGO	16 41.02%	8 14.81 %	
Consolidation	8 20.51 %	15 27.77 %	4 33.3%
Mixed GGO and consolidation	15 38.46 %	31 57.4 %	8 66.6%
Pleural effusions		4 7.4 %	

DISCUSSION

The search for universal ways to assess different prognostic markers and care strategies are continuing. In the present study, a normal Hb level was found in 66 patients (63%), a finding which is supported by Fan et al (2020) **[14]**. Lippi et al reported a substantially reduced Hb level in patients with severe disease which agrees with our finding in which Hb level was statistically significant lower in dead than recovered patients **[15]**.

In contrast to ICU admission, there was no relationship between Hb level, whether normal or low and ICU admission. However, when mechanical ventilation was considered, more patients with low Hb were ventilated than those with normal levels.

Our study revealed no statistically significant difference between dead and recovered (**7**.01 ± 0.43, 7.41 ± 0.78) as regarding total leucocytic count although seven patients with leucocytosis died constituting 25% from all dead patients, this highlights the prognostic impact of leucocytosis on death in COVID -19 patients as it is the hallmark of inflammation. In the present study, the LMR was statically significantly higher in patients who died versus recovered (4.27±0.47 vs 3.3 ± 0.22) and lymphocytopenia was found in 91 (87%) of our patients. We could explain the cause of lymphocytopenia to their excessive fragility and disruption as many smudged cells were found in blood smears and they were not counted by automated cell counters among lymphocytes. In agreement with our findings, Pezeshki et al reported on the presence of smudged cells in COVID-19 patients **[16]**. Wagner et al supported the concept that lymphocytopenia can be an early, valuable, and easily obtainable prognostic indicator in determining the clinical course and severity of a COVID-19 patient **[17]** while Daria et al reported that a low LMR on admission was associated with progressive pneumonia **[18]**.

As regards the platelet count, thrombocytopenia (a value < 150,000 /cmm) was found in 11 patients (10%) which agrees with Fan et al who detected that most of their patients had normal platelet counts, with 13 patients (20.0%) having mild thrombocytopenia **[14]**. The fact that only three thrombocytopenic patients died does not incriminate thrombocytopenia as a causal for death. Wool & Miller stated that COVID-19 patients have mild thrombocytopenia due to enhanced platelet consumption **[19]**. On the contrary, seven patients in our study were suffering from thrombocytosis (a value >450,000 /cmm), five of them died and three were mechanically ventilated which makes thrombocytosis carry a higher mortality risk than thrombocytopenia. We can explain this discrepancy to the substantial pro-inflammatory function of the platelets. Myocardial infarction was the cause of death of one of our patients as proven by raised cardiac troponin and ECG findings, his platelets were 960,000/cmm with D-Dimer value over 400 ng/ml. This reflects the dismal impact of thrombocytosis in COVID-19.

Our present study showed significantly increase D-Dimer in dead patients compared to recovered one (362.96 ± 31.52 , 190.81± 12.49) (p=0.00) a finding which agrees with Wool & Miller **[19]** who correlated the risk of mortality with elevated D-Dimer as D-dimer levels are most likely indicative of pulmonary vascular bed thrombosis and fibrinolysis[20]. D-dimers reflect fibrin clot formation, FXIIIa-mediated clot crosslinking, and fibrinolysis. The significant increase in D-dimers in COVID-19 appears to be due to coagulation activation caused by viremia and cytokine storm, but superinfection and organ dysfunction are also possibilities **[19].**

The current study showed statically significant increased ferritin level in dead patients than recovered (490.3 ± 45.92, 278.72 ± 16.84) (p=0.00) that can be explained as ferritin is a critical modulator of immunological dysregulation, particularly in extreme hyperferritinemia, through direct immune-suppressive and pro-inflammatory actions **[21]**.

The mean EASIX in recovered patients was 1.78 ± 1.17 versus 3.47 ± 0.45 in those who died.

The difference was highly statistically significant which was in accordance with Zinczuk et al findings **[22]**.

By discussing our results as regards D-Dimer, ferritin, EASIX, and LMR as a prognostic determinant of mortality and ICU admission, we found that they were a delicate parameter as they showed a statistically significant sensitivity and specificity. But need for mechanical ventilation was more correlated with D-Dimer, ferritin and EASIX as LMR was statically insignificant. Elkhalifa **[23]** results were in consistence with our findings as he stated that D-dimer mean values were considerably higher in COVID-19

patients who died and in ICU patients. He suggested that this biomarker may be useful as a predictor and prognostic indicator of severity, especially for COVID-19 patients who end up in the ICU.

Cheing et al. **[24]** realised that ferritin was found to be a useful indicator as it is linked to disease severity, mortality, and responses to treatment in COVID-19 patients. Hence, ferritin can predict the deterioration and was associated with a poor prognosis.

Thomas et al. **[25]** concluded that EASIX is a useful indicator that can predict the destiny in COVID-19 patients as they founded that it is simple to examine, which accords with our findings. More advanced study performed by Zinczuk, Rorat **[22]** confirmed the accuracy of EASIX and two of its modifications in predicting ICU admission, invasive mechanical ventilation requirement, and death occurrence from COVID-19.

Kosidlo et al. **[26]** briefly describe the role of LMR in the diagnosis of COVID-19, and note its potential use in predicting patient outcome in their literature review.

The remaining studied biochemical markers; CRP, LDH, AST/ ALT ratio and urea showed statically significant increase in died patients. This agrees with the findings of both Biamonte et al [27] & Medetalibeyoglu et al [28] in which the latter found also that ALT-AST elevation and AST/ALT ratio >1 were associated with more severe course and increased mortality in COVID-19.

Concerning the CT findings, they were differed according to disease stage and severity. Recovery was reported in 40%, 49% and 11% in early, progressive and advanced diseases respectively. GGO (41.02%) were mostly seen in the early stage and lesions were mainly located at the sub-pleural region in the lung periphery; this distribution may be due to the fact that virus particles fuse with the alveolar epithelium when they reach the cortical lobules in the lower lungs. In the progressive stage, expansion of the lesion area is typically seen, with frequent involvement of multiple lung lobes. This is mainly due to the collapse of alveolar walls and the replacement of air in the alveoli with inflammatory exudate, cells, or tissue.

The study by Chung et al presented similar findings to our study with GGO representing the common findings in the lungs **[29]**. Pan et al demonstrated preponderance of ground glass abnormality in early disease, followed by development of crazy paving and, finally, increasing consolidation later in the disease course making chest CT a hallmark of COVID-19 infection diagnosis **[30]**.

Regarding ECG findings, all patients with normal ECG recovered and 17/28 patients (60.7%) died as well as 11/28 (39.3%) died of CAD as one of mortality causes in COVID-19 patients. This obviates that ECG is not inferior to Echo. It is even preferred as it could be safer for the operator in facing this highly contagious disease. The cardiac causes of death in COVID-19 are mainly coronary artery thrombosis or myocarditis which manifests by left ventricular dysfunction on Echo **[31]**.

Limitation of the study: limited number of patients and the effect of vaccination that can change the disease course and affects the rate of morbidity and mortality.

CONCLUSION

Because of its strong correlation with COVID-19 mortality, we concluded that ESAIX should be added as a new biomarker to the existing set of biomarkers linked to poor prognosis, which already includes CBC analysis (leucocytosis, anaemia, and thrombocytosis), D-Dimer, ferritin, and LMR.

We also suggested using a combination of these inexpensive and simple-to-use biochemical indicators (EASIX, D-Dimer, ferritin, and LMR) to provide a more accurate prognosis determine for COVID-19 severity .

Adding value of the study validation of risk assessment by simple and handy indices.

Availability of data and materials: All data generated or analyzed during this study are included in this article.

Acknowledgements: Not applicable.

Conflicts of interest/Competing interests: The authors declare that they have neither conflict of interest nor competing of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics information. Ethics approval and consent to participate written informed consent was

obtained from all study subjects. Also, approval of the Research Ethics Committee of the Medical Research Institute (Ethics code: S/N. R14/2021), Alexandria University, Egypt, was obtained prior to the study. All procedures performed in our study were in accordance with the ethical standards of our institution and national and with the 1975 Helsinki declaration as revised in 2008.

HIGHLIGHTS

- Focus on finding a new easier and simpler predictor for COVID -19 severity than that studied before.
- Correlate ESAIX to mechanical ventilation, ICU admission and mortality as an end points in COVID 19 patients.
- EASIX should be combined with D-Dimer and ferritin as reliable prognostic determinants of COVID-19.

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Cite as: Feissal Rabie, M., Gaber, M., Soula, M., Masoud, I. Endothelail and Stress Index as One of New Prognostic Determinants of COVID- 19 Severity. *Afro-Egyptian Journal of Infectious and Endemic Diseases*, 2023; 13(2): 101-113. doi: 10.21608/aeji.2023.206428.1287