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Predictive Value of Rapid Scoring Systems and Laboratory Markers in Mortality in Critically ILL Patients with COVID-19: A Prospective Cross-Sectional Study

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ABSTRACT

Background: Coronavirus Disease of 2019 (COVID-19) is a global epidemic with thousands of deaths.

Objective: This work aimed to compare the prognostic value of rapid scoring systems; the Modified Early Warning Score (MEWS) and Rapid Emergency Medicine Score (REMS) with laboratory markers for mortality in critically ill patients with COVID-19 presenting to the ED.

Patients and Methods: This prospective cross-sectional study included a total of 92 patients with confirmed COVID-19, attending the Department of Emergency Medicine, Suez Canal University Hospital, during the period from April 1, 2022, to Oct 1, 2022.

Results: D-Dimer was with sensitivity (88%) and specificity (79%) at admission and sensitivity (96%) and specificity (86%) at follow-up; C-reactive protein (CRP) was with sensitivity (96%) and specificity (59%) at follow-up; ferritin was with sensitivity (87%) and specificity (56%) at admission and sensitivity (88%) and specificity (64%) at follow-up; IL-6 was with sensitivity (67%) and specificity (60%) at admission and sensitivity (96%) and specificity (87%) at follow-up; Lactate dehydrogenase(LDH) was with sensitivity (96%) and specificity (60%) at follow-up; and procalcitonin (PCT) was with sensitivity (80%) and specificity (56%) at follow-up. There was a significant difference between both groups regarding the median of MEWS (4 vs. 3, $p = 0.004$) and REMS (9 vs. 6, $p<0.001$) that were higher in non-survivors than survivors.

Conclusion: REMS was better than the MEWS score in predicting mortality. Also, D-dimer at admission and follow-up, CRP at follow-up, ferritin at admission and follow-up, IL-6 at admission and follow-up, LDH at follow-up, and PCT at follow-up could be used for the prediction of mortality better than rapid scoring systems.

Keywords: Severity of illness index, Patient acuity, COVID-19, Risk factors.

INTRODUCTION

2019 saw the identification of a new coronavirus as the cause of pneumonia in Wuhan, China. On February 2020, the WHO classified the illness as COVID-19. SARS-CoV-2 is the virus that causes COVID-19 [1]. According to reports, the death rate for COVID-19 patients in critical condition varies between 11% and 61% [2].

To reduce the mortality rate of critically ill COVID-19 patients by prompt medical care, emergency physicians must swiftly identify severely affected patients from a large pool of patients [3].

To standardize the treatment of patients in the emergency department (ED), several researchers have focused on physiologic scoring approaches for the quick identification of high-risk patients. The MEWS was one of these point systems [4].

The REMS is another scoring methodology that was just introduced. When nonsurgical patients were admitted to the ED, the REMS model was first suggested as a way to forecast their death [5].

It is easy to evaluate and compute the score based on the limited number of basic variables that have been included in the REMS and MEWS models in ED [6]. Procalcitonin (PCT), serum ferritin, CRP, elevated neutrophil count, elevated D-dimer readings, lymphopenia, and elevated procalcitonin are the main characteristics used to distinguish between individuals with mild and severe COVID-19. Severe COVID-19 individuals may have dramatic changes in other inflammatory cytokines, such as liver enzymes, IL-6, LDH, and kidney function tests [7]. The purpose of the study was to compare the prognostic value of rapid scoring systems (MEWS and REMS) with laboratory markers for mortality in critically ill patients with COVID-19 presenting to the ED.

PATIENTS AND METHODS

This prospective cross-sectional study included a total of 92 patients with confirmed COVID-19, attending at Department of Emergency Medicine, Suez Canal University Hospital, during the period from April 1, 2022, to Oct 1, 2022.

All participants were identified as COVID-19 patients, according to the WHO and the Egyptian Ministry of Health and Population[8]. Patients were excluded if they were not admitted, were transferred to another institution, or for age <18 years.

Data collection:

Patients were initially assessed, including temperature, respiratory rate, pulse, and oxygen saturation. A data collecting sheet was used to gather the data. The diagnosis was confirmed by symptoms with a positive PCR test for SARS-CoV-2 and CO-RAD score of ≥5. Laboratory markers were performed including liver and kidney function tests, a CBC with differential, CRP, ferritin, LDH, D-dimer, and an electrocardiogram.

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All of the variables required to calculate the REMS and MEWS models were included in these data. Based on MAP, PR, RR, oxygen saturation, GCS, and patient age, individual REMS scores were computed.

Similarly, HR, SBP, RR, body temperature, and awareness were used to determine each MEWS individual score. A hospitalized patient's death was referred to as a case fatality.

Ethical approval:

Suez Canal University, Medical Ethics Committee of the Faculty of Medicine gave its approved this study [Approval # 4813; Approval date Feb 6, 2022], and the paper complies with STROBE principles. To participate in the study, individuals or their surrogates had to provide written informed consent. The Helsinki Declaration was adhered to at every stage of the investigation.

Statistical analysis

Data collection and statistical analysis were conducted using IBM® SPSS Statistic ver. 24 (IBM Corp., Armonk, USA). Estimates of mean±SD, specificity, and sensitivity were made. To evaluate the statistical difference between variables, the student t-test and chi-square test were employed. Tables and graphs provided an overview of the study's findings. When it is equal to or less than 0.05, a significant p-value is taken into account.

RESULTS

In this study, the observed in-hospital mortality rate was 33.7% (n = 31). Interestingly, mortality was higher in those with chronic liver disease and lower among those with a history of prior stroke (3%).

This study results showed that there was a significant difference between both groups regarding WBCs, neutrophils, serum creatinine at follow-up, ALT, and AST (at admission and at follow-up) that were higher in non survivors than survivors, and regarding monocytes at admission, lymphocytes at follow-up, and platelets at follow-up that were lower in non-survivors than survivors, as mentioned in tables 1 and 2.

Table (1): Hematological findings among the studied groups

Variables	Survivors (N=61)	Non-Survivors (N= 31)	t/X^2	P value
WBCs (mcL) at admission	10.04 ± 2.4	12.7 ± 2.8	-1.9	0.05
WBCs (mcL) at follow-up	7.7 ± 1.7	21.3 ± 5.1	-7.5	<0.000*
t, P	4.8, <0.0001*	-4.1, <0.0001*		
Neutrophils (x10^9/L) at admission	81.1 ± 12.1	84.06 ± 5.1	-1.3	0.19
Neutrophils (x10^9/L) at follow-up	74.01 ± 17.5	86.6 ± 4.8	-3.9	<0.000*
t, P	5.2, <0.0001*	-5.09, <0.0001*		
Monocytes (x10^9/L) at admission	6.4 ± 1.5	5.02 ± 1.1	2.49	0.01*
Monocytes (x10^9/L) at follow-up	7.25 ± 1.4	6.21 ± 1.2	1.91	0.05
t, P	-3.2, 0.001*	-3.4, 0.002*		
Lymphocytes (x10^9/L) at admission	7.09 ± 1.3	3.8 ± 0.8	1.42	0.15
Lymphocytes (x10^9/L) at follow-up	11.7 ± 2.8	4.3 ± 1.0	2.7	0.008*
t, P	-4.1, <0.0001*	-2.2, 0.03*		
PLT (x10^9/L) at admission	205.4 ± 50.4	181 ± 37.7	1.31	0.19
PLT (x10^9/L) at follow-up	228.5 ± 55.6	159.1 ± 38.2	3.9	<0.000*
t, P	-1.8, 0.06	2.7, 0.01*		

WBCs: white blood cells, PLT: platelet, t: t test, P value: probability test. *: Statistically significant (P < 0.05).

Table (2): Biochemical data among the studied groups

Variables	Survivors (N=61)	Non-Survivors (N= 31)	t/X^2	P value
ALT (U/L) at admission	46.6 ± 11.4	110.1 ± 25.9	-3.18	0.002*
ALT (U/L) at follow-up	48.3 ± 11.2	163.7 ± 38.9	-5.08	<0.0001*
t, P	-0.67, 0.5	-3.2, 0.003*		
AST (U/L) at admission	52.3 ± 12.7	230.7 ± 55.9	-3.6	0.001*
AST (U/L) at follow-up	52.7 ± 11.5	240.7 ± 56.8	-3.8	<0.0001*
t, P	-0.17, 0.86	-2.1, 0.04*		
S. Creatinine (mg/dl) at admission	1.49 ± 0.34	1.5 ± 0.35	-0.022	0.98
S. Creatinine (mg/dl) at follow-up	1.22 ± 0.30	2.16 ± 0.52	-3.61	<0.0001*
t, P	2.69, 0.009*	-4.1, <0.0001*		

ALT: Alanine aminotransferase, AST: aspartate aminotransferase, S. Creat: serum creatinine. t: t test, *: Statistically significant (P < 0.05).

The current study revealed that inflammatory markers showed significant differences between both groups regarding D-dimer, ferritin, and IL-6 at admission and after follow-up, and regarding CRP, LDH, and PCT after follow-up that were higher in non-survivors than survivors. Also, there was a significant difference in each group regarding inflammatory markers and D dimer at admission and at follow-up, except for LDH in the survivors' group and PCT in each group, as mentioned in table 3.

Table (3): Inflammatory markers and D dimer among the studied groups

Variables	Survivors (N=61)	Non-Survivors (N= 31)	t	P value
D-Dimer (ng/mL) at admission	0.61 ± 0.14	3.02 ± 0.61	-6.8	<0.0001*
D-Dimer (ng/mL) at follow-up	0.26 ± 0.05	24.7 ± 5.7	-4.4	<0.0001*
t, P	5.9, <0.0001*	-2.5, 0.01*		
CRP (mg/L) at admission	58.3 ± 14.3	40.6 ± 9.9	1.56	0.12
CRP (mg/L) at follow-up	7.08 ± 1.5	72.9 ± 17.8	13.8	<0.0001*
t, P	6.6, <0.0001*	-4.7, <0.0001*		
Ferritin (ng/mL) at admission	669.5 ± 164.8	1056.8 ± 261.7	-3.7	<0.0001*
Ferritin (ng/mL) at follow-up	446.7 ± 108.6	1225.5 ± 303.6	-9.1	<0.0001*
t, P	4.3, <0.0001*	-2.5, 0.01*		
IL-6 (pg/mL) at admission	236.6 ± 57.7	738.5 ± 183.2	-2.1	0.03*
IL-6 (pg/mL) at follow-up	5.3 ± 1.4	1043.7 ± 250.1	-5.8	<0.0001*
t, P	2.08, 0.04*	-2.3, 0.02*		
LDH (U/L) at admission	694.7 ± 171.2	614.5 ± 151.7	0.5	0.61
LDH (U/L) at follow-up	481.2 ± 118.3	846 ± 209.9	-5.66	<0.0001*
t, P	1.86, 0.06	-4.6, <0.0001*		
PCT (ng/mL) at admission	9.3 ± 2.2	23.4 ± 5.6	-1.25	0.21
PCT (ng/mL) at follow-up	0.18 ± 0.043	33.9 ± 8.2	-3.9	<0.0001*
t, P	1.88, 0.06	-0.82, 0.41		

D-Dimer: D-Dimer Protein, CRP: C reactive protein, IL-6: interleukin-6, LDH: Lactic Dehydrogenase, PCT: Procalcitonin.*: Statistically significant (P < 0.05).

Our study results revealed a substantial difference between the two groups in terms of CO-RAD score, with non-survivors scoring higher than survivors, as mentioned in table 4.

Table (4): CORAD and Discharge Date among the studied groups

Variables	Survivors (N=61)	Non-Survivors (N= 31)	U/X2	P value
CORAD	3 (2-4)	5 (3-5)	176	<0.0001
Discharge data	58 (95%)	1 (3%)	X2= 75.3	<0.0001*

CORAD: coronavirus disease 2019 (COVID-19) Reporting and Data System. *: Statistically significant (P < 0.05).

In this study, D-Dimer was used in the prediction of mortality with sensitivity (88%) and specificity (79%) at admission and sensitivity (96%) and specificity (86%) at follow-up. CRP was used in the prediction of mortality with sensitivity (58%) and specificity (48%) at admission and sensitivity (96%) and specificity (59%) at follow-up.

Ferritin was used in the prediction of mortality with sensitivity (87%) and specificity (56%) at admission and sensitivity (88%) and specificity (64%) at follow-up. LDH was used in the prediction of mortality with sensitivity (67%) and specificity (58%) at admission and sensitivity (96%) and specificity (60%) at follow-up. PCT was used in the prediction of mortality with sensitivity (61%) and specificity (50%) at admission and sensitivity (80%) and specificity (56%) at follow-up. IL-6 was used in the prediction of mortality with sensitivity (67%) and specificity (60%) at admission and sensitivity (96%) and specificity (87%) at follow-up, as mentioned in table 5.

In this study, REMS was better than MEWS score in prediction of mortality with AUC (0.817 versus 0.682), sensitivity (78% versus 77%), and specificity (72% versus 55%), as mentioned in table 5.

Table (5): Roc curve of different variables to predict mortality rate

Variable(s)	Area	Std. error	P value	Cut off	Sensitivity	Specificity
MEWS	0.682	0.057	0.005*	2.5	77%	55%
REMS	0.817	0.046	<0.0001*	6.5	78%	72%
D-Dimer at admission	0.831	0.048	<0.0001*	0.75	88%	79%
DIMER at follow-up	0.983	0.018	<0.0001*	0.45	96%	86%
CRP at admission	0.451	0.062	0.447	31	58%	48%
CRP at follow-up	0.961	0.021	<0.0001*	5	96%	59%
ferritin at admission	0.722	0.056	0.001*	576	87%	56%
Ferritin at follow-up	0.911	0.042	<0.0001*	521.5	88%	64%
IL 6 at admission	0.67	0.06	0.008*	9	67%	60%
IL 6 at follow-up	0.965	0.019	<0.0001*	5	96%	87%
LDH at admission	0.581	0.065	0.203	416	67%	58%
LDH at follow-up	0.822	0.044	<0.0001*	428	96%	60%
PCT at admission	0.514	0.072	0.83	0.22	61%	50%
PCT at follow-up	0.839	0.052	<0.0001*	0.15	80%	56%

ROC: Receiver-operating characteristic analysis for evaluating the accuracy of a statistical model logistic regression, linear discriminant analysis. *: Statistically significant (P < 0.05).

DISCUSSION

In this study, the prevalence of death was 33.7%, with a higher percentage of patients with chronic liver disease than non-survivors than survivors, while survivors had a significantly higher percentage of patients with previous stroke than non-survivors. This is in agreement with another study, which found that prevalence of death was 45%. The non-survivor group had a much greater level of comorbidity[9]. Another study showed that the prevalence of death was 18.1%, with comorbidities having a higher presence in non-survivors[10].

This study demonstrated a significant difference between the two groups. In terms of WBCs, neutrophils, serum creatinine at follow-up, ALT, and AST (at admission and at follow-up), which were higher in non-survivors than survivors, as well as in terms of monocytes at admission, lymphocytes at follow-up, and platelets at follow-up, which were lower in non-survivors than survivors. Comparable to the findings of the **Abdelhameed *et al.*** [9] research, which demonstrated that the non-survivor group's WBCs, urea, creatinine, bilirubin, and CRP were considerably greater than those of the survivors group. These findings were in line with the findings of **Li *et al.*** [11] research, which showed that there was a significant difference in WBCs, creatinine, and bilirubin levels between survivors and non-survivors. The non-survivor group also had fewer platelets.

According to the results of this investigation inflammatory markers showed significant differences between both groups regarding D-dimer, ferritin, IL-6, CRP, LDH, and PCT which were higher in non-survivors than survivors. Also, within each group, inflammatory markers and D-dimer showed significant change from admission until follow-up. Also, **Abdelhameed *et al.*** [9] study discovered that inflammatory markers (IL6, PCT, and ferritin) were significantly higher in the non-survivor group. (p = 0.15 ng/ml, 0.0815 for CRP >55 mg/L, and 0.5865 for D-dimer >0.5 ug/ml).

The findings of this study demonstrated a substantial difference in CORAD between the two groups, with non-survivors having a greater level than survivors. In a similar vein, the **Inanc *et al.*** [12] investigation discovered that patients with a CO-RADS score of 4 or above had a considerably greater 28-day mortality (97.3% vs. 2.7%; p<0.001) than patients with a score of 3 or below.

In this study, D-Dimer was used in the prediction of mortality with sensitivity (88%) and specificity (79%) at admission and sensitivity (96%) and specificity (86%) at follow-up. **Gungor *et al.*** [13], in a research conducted, determined that patients who had high D-dimer levels at the time of admission were at a greater risk of dying (relative risk of 1.82) and having a more severe condition (relative risk of 1.58).

In a research by **Kiss *et al.*** [14], COVID patients with D-dimer levels above 0.50 mg/L had a higher risk of death (OR=4.30 [CI 1.55, 11.98], p=0.005). **Poudel *et al.*** [15] recently found that d-dimer serum levels exhibited a sensitivity of 83% and a specificity of 70% in predicting mortality in COVID patients. However, **Cidade *et al.*** [16] research findings show that blood d-dimer levels at admission had a limited capacity to predict the survival of severe COVID-19 patients.

In this study, CRP was used in the prediction of mortality with sensitivity (58%) and specificity (48%) at admission and sensitivity (96%) and specificity (59%) at follow-up. According to a study by **Ikeagwulonu *et al.*** [17], which included 61 studies with a total of 13891 COVID-19 patients, CRP concertation has been identified as a severity indicator of COVID-19. Severe cases had consistently higher levels of CRP than mild cases, which was statistically significant in 78.7% of the cases.

In cohort research, **Smilowitz *et al.*** [18] found that CRP levels above 108 mg/L were linked to greater

mortality (32,2% vs. 17,8%) and a severity of illness (47,6% vs. 25,9%). Similar to this, a study by **Luo *et al.*** [19] shown that CRP, with a cut-off value of 41.4 and the maximum sensitivity of 95.4%, was a discriminator of severe or critical disease upon admission. Increased mortality was linked to baseline CRP levels over 10 mg/L and follow-up levels above 100 mg/L, according to the assessment of elevated CRP in the **Kiss *et al.*** [14] trial (OR = 4.84 [CI 1.49, 15.69], p = 0.009).

In this study, ferritin was used in the prediction of mortality with sensitivity (87%) and specificity (56%) at admission and sensitivity (88%) and specificity (64%) at follow-up. Similar to the **Lino *et al.*** [20] study, which showed that ferritin has a sensitivity of 68.4% and specificity of 79.3% in predicting in-hospital mortality. Ferritin levels ≥1873.0 ng/mL had an OR of 6.0 (95% CI = 1.4-26.2; p = 0.016).

In this study, LDH was used in the prediction of mortality with sensitivity (67%) and specificity (58%) at admission and sensitivity (96%) and specificity (60%) at follow-up. Similarly, **Kiss *et al.*** [14] reported that LDH levels over 250 U/L at admission were seen to be associated with a higher risk of death (OR = 10.88 [CI 4.48, 26.39], p < 0.001).

In this study, PCT was used in the prediction of mortality with sensitivity (61%) and specificity (50%) at admission and sensitivity (80%) and specificity (56%) at follow-up. **Kiss *et al.*** [14] study reported that procalcitonin levels beyond 0.05 ng/mL at baseline did not appear to be a risk factor for death; nevertheless, the analysis demonstrated increased risk above the 0.50 ng/mL threshold (OR = 11.97 [CI 4.75, 30.16], p < 0.001, I2 = 59.4%). In patients with COVID-19, elevated procalcitonin upon admission might not be a significant result. It's interesting to note that elevated PCT levels can predict death [21].

In this study, IL-6 was used in the prediction of mortality with sensitivity (67%) and specificity (60%) at admission and sensitivity (96%) and specificity (87%) at follow-up. **Gorham *et al.*** [22] performed research on individuals who were diagnosed with COVID-19. Compared to survivors, non-survivors' IL-6 values were substantially higher (720 vs. 336 pg/mL, p = 0.01). ICU mortality was significantly predicted by the highest IL-6 value (95% CI 0.57–0.89; p = 0.01).

The present study found that there was a significant difference between both groups regarding the median of MEWS (4 vs. 3, p = 0.004) and REMS (9 vs. 6, p<0.001) that were higher in non-survivors than survivors. REMS at cutoff point 6.5 was better than MEWS score at cutoff point 2.5 in prediction of mortality with AUC (0.817 versus 0.682), sensitivity (78% versus 77%), and specificity (72% versus 55%).

According to **Olsson *et al.*** [23], the REMS is a potent and easy measure that successfully predicts in-hospital mortality, as opposed to other ratings that are not ideal for early usage in patients brought to the emergency department. This is consistent with the findings of **Hu *et al.*** [10], who found a substantial difference in MEWS and REMS scores between survivors and those who did not survive.

Hu *et al.* [10] also showed that MEWS performed well in predicting in-hospital mortality, with a sensitivity and specificity of 68.42 and 65.12%, respectively. Similarly, the REMS was used to predict in-hospital mortality with a perfect cutoff value of 6, showing 89.47 percent sensitivity and 69.77 percent specificity. The difference between the two was found to be statistically significant (p = 0.028 < 0.05), even though the AUC of the REMS and MEWS models was 0.841 (95% CI = 0.757 to 0.905) and 0.677 (95% CI = 0.579 to 0.765), respectively, in predicting in-hospital mortality.

CONCLUSION

REMS was better than the MEWS score in predicting mortality. Also, D dimer at admission and follow-up, CRP at follow-up, ferritin at admission and follow-up, IL-6 at admission and follow-up, LDH at follow-up, and PCT at follow-up could be used for the prediction of mortality better than rapid scoring systems. The usage of these grading systems in ED can be a useful way for predicting the prognoses of patients. Also, laboratory markers such as ferritin, PCT, and LDH can be used in the prediction of disease severity at admission.

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