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Original article

Could De Ritis Score Be a Useful Predictor of Mortality in COVID-19 Patients Who Require Intensive Care?

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SUMMARY

Introduction/Aim. Inflammatory markers are being investigated as possible predictors of mortality in intensive care population. COVID-19 infection causes significant amount of inflammatory burden. De Ritis score has been suggested as a novel disease marker in conditions characterized with inflammation. In the present work, we aimed to compare De Ritis scores of deceased and survived COVID-19 patients in an institutional intensive care unit.
Methods. Patients treated in intensive care unit with a diagnosis of COVID-19 infection were enrolled in the study. De Ritis scores of the deceased and survived subjects were compared.
Results. The De Ritis score among survivors and non-survivors was 1.12 (range: 0.3–6.9)% and 1.43 (range: 0.2–16)%, respectively, with a statistically significant difference ($p = 0.03$). Additionally, the De Ritis score exhibited significant positive correlations with lactate dehydrogenase (LDH) ($r = 0.37$, $p < 0.001$), D-dimer ($r = 0.38$, $p < 0.001$), and C-reactive protein (CRP) ($r = 0.19$, $p = 0.01$) levels. When the De Ritis score exceeded the 1.32% threshold, its sensitivity and specificity in predicting mortality were 60% and 61%, respectively, with an area under the curve (AUC) of 0.61 ($p = 0.03$, 95% confidence interval: 0.52–0.7). Furthermore, each unit increase in the De Ritis score was associated with a 96% increase in the odds of mortality among COVID-19 patients treated in the intensive care unit ($p = 0.03$, OR: 0.96, 95% confidence interval: 0.86–0.98).
Conclusion. De Ritis score can be a useful marker of poor prognosis in COVID-19 patients in intensive care units.

Keywords: **De Ritis score, inflammation, COVID-19, intensive care**

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INTRODUCTION

Intensive care unit (ICU) serves as critical hubs for patients battling severe illnesses and life-threatening conditions. Within these high-stakes medical environments, one of the paramount concerns is mortality, as healthcare providers strive to improve patient outcomes. In recent years, there has been a growing recognition of the intricate relationship between mortality in the ICU and the use of inflammatory markers as valuable prognostic tools. Inflammation, a complex biological response triggered by the body in response to injury or infection, plays a central role in many critical illnesses. Consequently, monitoring inflammatory markers in ICU patients has emerged as a promising avenue for predicting outcomes, tailoring treatment strategies, and enhancing overall patient care. Recent research has uncovered a notable link between mortality among patients in the intensive care unit and elevated levels of inflammatory markers in the bloodstream. These markers encompass mean platelet volume (1), the ratio of C-reactive protein to albumin (2), and the systemic inflammatory index (3).

COVID-19 infection typically initiates with flu-like symptoms (4) and can manifest as asymptomatic or range from mild to severe in severity (5). The infection is characterized by a significant inflammatory burden (6). Research has investigated the association between hemogram parameters and COVID-19 infection, revealing that neutrophil to lymphocyte ratio (NLR) (7) and several other inflammation markers (8) are linked to the infection. Additionally, red cell distribution width, an indicator of anisocytosis in the hemogram, has been linked to recurrent hospitalizations in COVID-19 patients (9). Furthermore, certain inflammatory markers have been identified as predictors of frailty in diabetic individuals during COVID-19 (10). Hence, it can be inferred that inflammatory indices may be correlated with COVID-19 infection.

The De Ritis score, named after the Italian physician Fernando De Ritis, is a widely used diagnostic tool in the field of clinical medicine (11). This simple yet informative score is primarily employed to assess liver function and help diagnose various liver-related disorders. By examining the ratio of two essential enzymes in the bloodstream, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT), the De Ritis score offers valuable insights into the health and functioning of the liver. In this introduction, we will delve into the significance of the De Ritis score, its calculation, and its crucial role in aiding medical professionals in diagnosing and monitoring liver diseases. It has been linked to inflammatory conditions i.e., thyroiditis (12). Moreover, it has been linked with renal and respiratory dysfunction (13) and mortality (14).

In this retrospective study, our objective was to compare the De Ritis scores of intensive care patients who survived with those of deceased subjects.

PATIENTS AND METHODS

Following the approval of the study protocol by the local Ethics Committee (approval date: August 22, 2023, approval number: 2023/274), we included COVID-19 patients from the intensive care unit in the current retrospective study. We analyzed the data of the patients treated in our institution between January 2021 till December 2021. The study group was divided according to the outcome—into survived and deceased patients' groups. Subjects younger than 18 years of age, with established acute/chronic liver disease, and pregnant women were excluded from the study. Age, gender, and the presence of comorbidities such as diabetes mellitus, hypertension, cancer, cardiovascular diseases, chronic obstructive pulmonary disease, and chronic kidney disease were recorded after retrieving data from patients' files and the institutional database. Laboratory parameters of the participants, including leukocyte count (WBC), hemoglobin (Hb), platelet count (PLT), blood urea, serum creatinine, plasma glucose, aspartate and alanine transaminases (AST, ALT), serum albumin, lactate dehydrogenase (LDH), D-dimer, ferritin, and C-reactive protein (CRP) values of the study population were noted. The De Ritis score is derived by dividing AST by ALT. Subsequently, data from both survived and deceased subjects were compared.

Statistics

Statistical analyses were performed using SPSS 18.0 for Windows (IBM Co., Armonk, NY, USA). The homogeneity of study variables was assessed using the Kolmogorov-Smirnov test. Continuous variables conforming to a normal distribution were presented as means and standard deviations and compared using independent t-test samples. Continuous variables not adhering to a normal dis-

tribution were presented as medians (range) and compared using the Mann-Whitney U test. Categorical variables were compared using the Chi-square test and expressed as percentages. Pearson's correlation analysis was conducted to explore potential correlations among study variables. Receiver operating characteristic (ROC) curve analysis was employed to determine the sensitivity and specificity of the De Ritis score in predicting mortality. Binary logistic regression analysis was utilized to ascertain whether the De Ritis score independently constituted a risk factor for mortality in the ICU population. Statistical significance was defined as a probability (p) value greater than 0.05.

RESULTS

Among the patients, there were 133 deceased individuals and 146 survivors. The mean ages of the survived and deceased subjects were 75 years (± 13) and 65 years (± 17), respectively ($p < 0.001$). Respectively, 59% and 63% of the survived and deceased patients were men ($p = 0.63$). Diabetes mellitus was found in 20% and 37% of the survived and deceased COVID-19 patients, respectively ($p = 0.03$). The rates of hypertension (65% in survivors versus 72% in deceased; $p = 0.41$), cancer (7% in survivors versus 14% in deceased; $p = 0.17$), cardiovascular diseases (30% in survivors versus 35% in deceased; $p = 0.57$), chronic obstructive pulmonary disease (11% in survivors versus 22% in deceased group; $p = 0.11$), and chronic kidney disease (7% in survivors versus 10% in deceased; $p = 0.43$) were similar in survived and deceased patients.

Median De Ritis score of the survived and deceased subjects were 1.12 (0.3–6.9)% and 1.43 (0.2–16)%, respectively. De Ritis score was significantly higher in deceased group compared to the survived group ($p = 0.03$). Data of the survived and deceased groups were summarized in Table 1.

The De Ritis score exhibited significant positive correlations with LDH ($r = 0.37$, $p < 0.001$), D-dimer ($r = 0.38$, $p < 0.001$), and CRP ($r = 0.19$, $p = 0.01$) levels.

In the ROC analysis, when the De Ritis score exceeded the 1.32% threshold, it demonstrated a sensitivity of 60% and specificity of 61% in predicting mortality, with an AUC of 0.61 ($p = 0.03$, 95% confidence interval: 0.52-0.7). Figure 1 illustrates the ROC curve of the De Ritis score for mortality detection.

Table 1. *Data of the deceased and survived COVID-19 patients in intensive care unit*

	Deceased	**Survived**	p
	Mean ± SD		
Age (years)	75 ± 13	65 ± 17	**< 0.001**
Hb (Hb)	13.4 ± 1.3	13.3 ± 1.5	0.64
Serum albumin (g/dL)	2.8 ± 0.5	3.2 ± 0.6	**0.001**
	Median (min-max)		
WBC (k/mm^3)	12.4 (0.5-48)	11 (2.8-36)	0.13
PLT (k/mm^3)	187 (27-618)	230 (29-505)	**0.02**
LDH (U/L)	524 (230-1500)	449 (219-1041)	**0.03**
D-dimer (mg/L)	3 (0.3-72)	3 (0.2-75)	0.3
Ferritin (ng/mL)	789 (21-2000)	490 (19-2000)	**0.004**
CRP (mg/L)	112 (0.5-350)	68 (0.1-344)	**0.003**
Urea (mg/dL)	71 (17-396)	47 (17-186)	**< 0.001**
Creatinine (mg/dL)	1.2 (0.4-11.4)	0.9 (0.4-8.3)	**0.001**
Glucose (mg/dL)	148 (69-618)	133 (75-415)	0.12
AST (U/L)	46 (7-2730)	38 (13-428)	**0.03**
ALT (U/L)	34 (6-1344)	39 (8-87)	0.87
De Ritis score (%)	1.43 (0.2 -16)	1.12 (0.3-6.9)	**0.03**

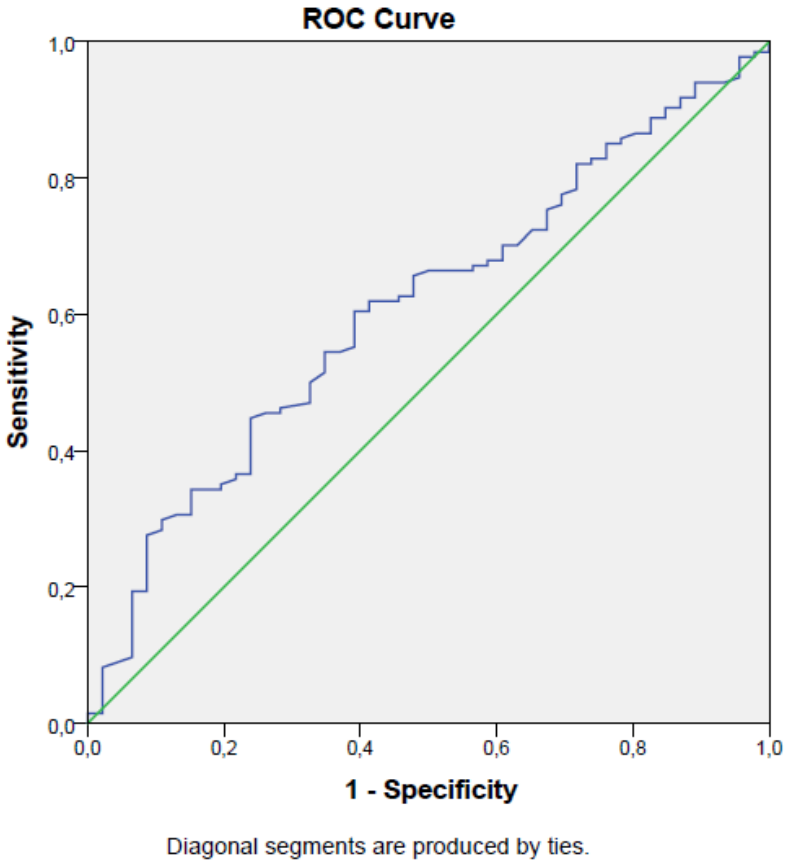

Figure 1. *ROC curve of De Ritis score in detecting mortality in ICU COVID-19 patients*

In binary logistic regression analysis, after adjustment of age, lactate dehydrogenase (LDH), ferritin, CRP and D-dimer, De Ritis score was found to be an independent risk factor for mortality in ICU population (p = 0.03, OR: 0.96, 95% confidence interval: 0.86-0.98). An increment of one unit in the De Ritis score elevated the odds of mortality by 96% among COVID-19 patients undergoing treatment in the intensive care unit.

DISCUSSION

The present study showed that De Ritis score could be a useful marker of mortality in ICU population with COVID-19 infection, since it is significantly increased in deceased subjects compared to the survivors. Furthermore, the De Ritis score showed a significant correlation with other inflammation markers such as CRP, LDH, and D-dimer. Additionally, notable sensitivity and specificity were observed in using the De Ritis score to predict mortality. Finally, regression analyses revealed that De Ritis score was an independent risk factor of mortality in ICU patients.

Inflammation is associated with COVID-19 infection (6). Higher burden of inflammation is noted in subjects with more serious disease course. Moreover, advanced elevation in inflammatory markers was noted in COVID-19 patients with poor outcome (15). De Ritis score is also elevated in conditions characterized with inflammation. Several examples may include malignant diseases (16), viral infections (17), sepsis (18), cerebrovascular diseases (19), and cardiac conditions (14). Given the association between COVID-19 infection and inflammation, the higher De Ritis scores observed in deceased patients compared to survivors in the present study align with existing literature findings.

Albitar et al. studied mortality risk factors in COVID-19 patients and found that male gender, older age, presence of diabetes mellitus, and hypertension independently increased the risk of mortality

in this population (20). Moreover, a meta-analysis revealed similar results by reporting advanced age, male gender, and accompanied chronic diseases as factors associated with mortality (21). Having diabetes mellitus was indeed an important factor that was associated with mortality in COVID-19 patients, according to the study by Shi et al. (22). Besides advanced age and male sex, a number of clinical factors including impaired kidney function, hypotension, tachypnea, hypoxia, elevated D-dimer, and elevated troponin were reported to be associated with COVID-19 mortality (23). Similarly, we found that deceased subjects were older, had higher serum creatinine levels and more frequently had the associated diabetes mellitus. Nevertheless, in our study, there were no significant differences in gender and D-dimer levels between deceased and survived patients. Additionally, comorbidities such as hypertension, cancer, cardiovascular diseases, chronic obstructive pulmonary disease, and chronic kidney disease were present in both the survived and deceased groups at similar rates, with no significant variation.

In the current study, serum CRP levels were elevated in the deceased subjects compared to the survivors. There are similar reports in the literature. High levels of CRP were reported in severe COVID-19 infection (24). Progression and severity of COVID-19 infection are well predicted with serum CRP levels, according to the Yitbarek et al's study (25). Subsequently, their findings were confirmed by another report (26). These data suggest that CRP was associated with severe cases of COVID-19. Our data further showed that CRP was associated with mortality in this population.

We observed higher LDH and ferritin levels in deceased COVID-19 patients when compared to those who survived. Poor prognosis was noted in a meta-analysis (27) in COVID-19 cases with elevated LDH levels. Furthermore, increased LDH was suggested as an independent risk factor for mortality in COVID-19 infection (28). Similarly, authors found serum ferritin as a reliable marker of inflammation and disease severity in COVID-19 patients (29, 30). These data are confirmed by our report and we further revealed that De Ritis score was correlated with CRP, LDH and D-dimer levels in COVID-19 population.

There are several limitations of the present work. First, retrospective design allows us only to clarify a simple association rather than causal relationship between COVID-19 mortality and De Ritis score. Second, single center nature of our study makes it difficult to globalize the study results. Third, a relatively small study population could be another limitation. However, this is one of the first studies reporting the association between De Ritis score and COVID-19 mortality in patients who required management in intensive care unit.

CONCLUSION

In conclusion, we find that the De Ritis score could make a useful, inexpensive, and easy to assess tool in determining the mortality risk of COVID-19 patients.

Authorship

IK and KII participated in the conception and design of the study, data collection and analysis, interpretation of the findings, drafting of the manuscript, and critical revisions for important intellectual content, and provided the final approval. BO and GA contributed to the conception and design of the study, analysis and interpretation of the data, drafting of the manuscript, critical revisions for important intellectual content, and provided the final approval. DRS contributed to critical statistical revisions of the manuscript for important intellectual content and provided the final approval.

Data availability statement

The data related to this work is available by the corresponding author upon reasonable requests.

Conflict of Interest

None to declare.

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Da li bi De Ritisov skor mogao biti koristan prediktor mortaliteta kod bolesnika sa kovidom 19 na intenzivnoj nezi?

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SAŽETAK

Uvod/Cilj. Markeri inflamacije istražuju se kao mogući prediktori mortaliteta kod bolesnika na intenzivnoj nezi. Infekcija kovidom 19 predstavlja značajan uzrok inflamacija. De Ritisov skor je predložen kao nov marker bolesti u uslovima karakterističnim za upalu. Cilj ovog rada bilo je upoređivanje De Ritisovih skorova kod bolesnika preminulih nakon komplikacija izazvanih kovidom 19 i bolesnika koji su preživeli infekciju kovidom 19 u institucionalnoj jedinici intenzivne nege.
Metode. Studija je obuhvatila bolesnike lečene u jedinici intenzivne nege sa dijagnozom infekcije kovidom 19. Upoređivani su rezultati De Ritisovog skora bolesnika koji su preminuli i bolesnika koji su preživeli.
Rezultati. De Ritisov skor među preživelim i preminulim bolesnicima bio je 1,12 (opseg: 0,3%–6,9%) i 1,43 (opseg: 0,2%–16%), redom, sa statistički značajnom razlikom (p = 0,03). Pored toga, De Ritisov skor pokazao je značajne pozitivne korelacije sa nivoima laktat dehidrogenaze (LDH) (r = 0,37, p < 0,001), D-dimera (r = 0,38, p < 0,001) i C-reaktivnog proteina (CRP) (r = 0,19, p = 0,01). Kada je De Ritisov skor premašio prag od 1,32%, njegova osetljivost i specifičnost u predviđanju smrtnosti bili su 60% i 61% za bolesnike koji su preminuli i one koji su preživeli, redom, sa površinom ispod krive (engl. *area under curve* – AUC) od 0,61 (p = 0,03, 95% interval pouzdanosti: 0,52–0,7). Štaviše, svako povećanje jedinice u De Ritisovom skoru bilo je povezano sa povećanjem šanse za smrtnost od 96% među bolesnicima sa kovidom 19 lečenim na odeljenju intenzivne nege (p = 0,03, OR: 0,96, 95% interval pouzdanosti: 0,86–0,98).
Zaključak. De Ritisov skor može biti koristan marker loše prognoze kod bolesnika sa kovidom 19 u jedinicama intenzivne nege.

Ključne reči: **De Ritisov skor, inflamacija, kovid 19, intenzivna nega**