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Role of Serum Lactate and CRP as Prognostic Markers in COVID-19

GEHAN A. ELDESOKY, M.D. and FATMA MOHAMED ABDELAZIZ, M.D.

The Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine for Girls, Al-Azhar University

Abstract

Background: Coronavirus disease (COVID-19) started its spread all over the world from Wuhan, China in December 2019, spreading very rapidly in all parts of the world Early diagnosis of severe cases aid in taking the best treatment decisions and decrease mortality.

Aim of Study: Assessment role of serum lactate and CRP in predicting the prognosis of hospitalized sever cases of COVID-19.

Patients and Methods: In this retrospective study, we evaluated 42 sever COVID-19 patients in total. They were divided into two groups group1 (survived) (n=23) and group 2 (non-survived) (n=19). Evaluation of inflammatory parameters total leukocyte count (TLC), absolute lymphocyte count (ALC), CRP and serum lactate were done.

Results: The non-survived patients suffered from respiratory acidosis. Serum lactate was significantly increased in group 2 than group 1 (p<0.05). CRP were significantly highly increased in group 2 than group 1 (p<0.001). Receiver operating characteristics (ROC) curve was done to determine the diagnostic power of serum lactate and CRP in differentiating COVID-19. Serum lactate revealed an AUC of 0.73 with sensitivity 63.2% and specificity 82.6% at cut-off value 2.6. Regarding CRP revealed an AUC of 0.85 with sensitivity 94.7% and specificity 73.9% at cut-off value 77. Multi-ROC between serum lactate and CRP revealed an improvement in the discrimination power with sensitivity 84.2% and specificity 82.6%.

Conclusion: Serum lactate and CRP are useful markers in predicting the prognosis of hospitalized sever cases of COVID-19. Dual assessment of serum lactate and CRP gave the best discrimination than the use of each of them alone.

Key Words: *COVID-19 – Inflammatory markers – Predicting prognosis.*

Introduction

COVID-19 is catastrophic public health crisis. The pathogenesis of COVID-19 started by attachment of virus to special receptors (angiotensin-converting enzyme-2) (ACE) receptors on multiple types of cells including lymphocyte, renal epithelial cells and type 2 pneumocytes [1]. The rapid viral replication and cellular destruction produce excessive inflammation and uncontrolled immune activation. Furthermore, the severe systemic immune response caused by a "cytokine storm is essential cause of development of multiple organ failure and acute respiratory distress syndrome (ARDS) [2].

Various laboratory biomarkers such as lymphocyte count, CRP, D dimer, ESR, interleukin 6, serum lactate, serum albumin and other inflammatory markers have been investigated for predicting the severity of COVID-19 and stratify them to guide medical management [3].

Our study aimed to assess the role of some inflammatory markers in predicting the prognosis and estimating the severity of COVID-19 patients. Our study hypothesized the prognostic capability of TLC, lymphopenia, serum lactate and CRP in predicting clinical outcomes.

Patients and Methods

This is a retrospective randomized clinical study that was carried out at Al-Zahraa University Hospital between April 2021 to July 2021.

The recruited patients (20-80) years was confirmed to be COVID-19 infection by RT-PCR. Severity of COVID-19 infection was confirmed as patients who had any of the following characteristic's at the time of admission: (1) Oxygen saturation ‹ 93% (2) Respiratory rate › 30 breaths per min (at rest), (3) PaO2 to FiO2 ratio ‹ 300 mmHg, (ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air) or (4) Specific complications, such as septic shock, respiratory failure, and or multiple organ dysfunction. Patients were excluded only if data was incomplete.

Correspondence to: Dr. Gehan A. Eldesoky,
E-Mail: drgihanabdelrhman@gmail.com

Demographic data of patients such as age, gender, weight and comorbidities were recorded. initial CT results defined by CO-RADS score from 1 to 5. Assessment of the patients included: Detailed medical history, previous medication, complete physical examination, and routine investigations. At time of admission, evaluation of inflammatory and immunological parameters such as total leukocyte count (TLC), absolute lymphocyte count (ALC), CRP and serum lactate have been analyzed.

The relation of the patients recorded data to individual survival was examined. The correlation of lymphopenia, CRP and serum lactate in predicting clinical outcomes were analyzed in terms of sensitivity and specificity.

Statistical analysis:

The recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). The Quantitative data were expressed as mean ± standard deviation (SD) and Qualitative data were expressed as frequency and percentage.

Results

The present retrospective study involved 42 patients that were recruited from ICU isolation partition at Al-Zahraa University Hospital. Patients were closely observed and monitored until they were discharged. Twenty-three of them survived and nineteen didn't survive. Hence the recruited patients were divided into 2 groups; Group 1 (survived) and Group 2 (non-survived). Demographic characteristics (age, sex and weight), Co–morbidities, are represented in Table (1). Biochemical parameters of the studied groups are represented in Table (2). The studied groups were matched in the baseline characters.

There were no significant differences in both groups according to their baseline characteristics regards age, sex and weight as shown in Table (1). There was a highly significant difference between both groups regarding hospital stay where the non-survived patients stayed less than the survived patients (p-value <0.001).

Regarding PH it shows highly statistically significant difference between both groups (p-value <0.01) as PH showed acidosis in non-survived (group 7.32±0.10) while in survived group it was normal (7.42±0.09) as shown in Table (2).

As regard pco2 was increased in non-survived group (30.79±4.29) than survived (28.30±5.16) with non-statistically significant difference between both groups (p-value>0.05) so patients in non-survived group showed respiratory acidosis.

Regarding po2 it was decreased in non-survived group (60.63±10.84) than survived (61.39±10.82) with non-statistically significant difference between both groups (p-value >0.05) so patients in non-survived group showed more hypoxia.

Regarding Hco3 it was decreased in non-survived group 22 (16.6-31) than survived 24.2 (21-31) with non-statistically significant difference between both groups (p-value >0.05).

Regarding Spo2 it was decreased in non-survived group (86.37±5.78) than survived one (89.30±5.26) with non-statistically significant difference between both groups (p-value >0.05). so, patients in non-survived group showed more hypoxia.

Table (1): Demographic data of studied groups.

Demographic data	Group 1 Survived No.=23	Group 2 Non-survived No.=19	Test value	p-value	Significance
Age (years):					
Mean ± SD	57.91±14.01	65.74±12.67	–1.881	0.067	NS
Range	30-75	43-92			
Sex:					
Female	11 (47.8%)	10 (52.6%)	0.096	0.757	NS
Male	12 (52.2%)	9 (47.4%)			
Weight (kg):					
Mean ± SD	89.83±14.22	88.58±8.18	0.338	0.737	NS
Range	70-140	75-110			
Hospital stays:					
Median (IQR)	6 (5-8)	2 (1-6)	–3.306	0.001	HS
Range	3-30	1-12			

Table (2): Arterial blood gases of the studied groups (ABG).

	Group 1 Survived No.=23	Group 2 Non-survived No.=19	Test value	p-value	Significance
PH:					
Mean ± SD	7.42±0.09	7.32±0.10	3.265	0.002	HS
Range	7.16-7.54	7.15-7.54			
PCO2:					
Mean ± SD	38.2±14.27	42.11±21.87	0.693	0.492	NS
Range	19-88	16-90			
PO2:					
Mean ± SD	61.39±10.82	60.63±10.84	0.226	0.822	NS
Range	43-85	44-85			
HCO3:					
Median (IQR)	24.2 (21-31)	22 (16.6-31)	1.519	0.129	NS
Range	16-88	6.5-88			
SPO2:					
Mean ± SD	89.30±5.26	86.37±5.78	1.722	0.093	NS
Range	79-96	70-94			

As regard TLC it was increased in non-survived group 14.3 (5-20) than survived 8.8 (4.2-13) with non-statistically significant difference between both groups (p-value >0.05) so patients in non-survived group showed septicemia as shown in Table (3).

Regarding lymphocytes as represented in Table (3) there was non-statistically significant difference between both groups however lymphopenia was more in survived group 1.2 (0.7-2) than non-survived one 1.2 (0.8-3).

In Table (3) regarding serum lactate there was statistically significant difference between both groups (p-value <0.05) as it was significantly increased in non-survived group 4 (2-6.2) than survived one 2 (1.6-3.4).

CRP was a highly statistically significant difference between both groups (p-value <0.01) as it was significantly increased in non-survived 112 (95-154) group than survived one 55 (40-89) as shown in Table (3).

Table (3): Inflammatory markers of both groups.

	Group 1 Survived No.=23	Group 2 Non-survived No.=19	Test value	p-value	Significance
TLC:					
Median (IQR)	8.8 (4.2-13)	14.3 (5-20)	–0.948	0.343	NS
Range	2.3-85	2.2-83			
Lymphocytes:					
Median (IQR)	1.2 (0.7-2)	1.2 (0.8-3)	–0.202	0.840	NS
Range	0.4-95	0.5-82			
Serum lactate:					
Median (IQR)	2 (1.6-3.4)	4 (2-6.2)	–2.444	0.015	S
Range	1-4.7	0.5-7			
CRP:					
Median (IQR)	55 (40-89)	112 (95-154)	–3.893	0.000	HS
Range	2.6-156	43-172			

p-value >0.05: Non-significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.

Patient outcomes of the studied groups during their hospital stay are represented in Fig. (1). 52.6% of group 2 suffered from Stroke / Cardiopulmonary complications, versus 21.7% only in group 1which is statistically significant difference.

Moreover, 57.9% of Group 2 required mechanical ventilation versus 13% only in group1 which is statistically highly significant difference.

In Fig. (1) receiver Operating Characteristics (ROC) curve of serum lactate for discrimination between survived and non-survived patients revealed an AUC of 0.733 with sensitivity 63.2% and specificity 82.6% at cut-off value 2.6. Receiver Operating Characteristics (ROC) curve of CRP for discrimination between survived and non-survived patients revealed an AUC of 0.852 with sensitivity 94.7% and specificity 73.9% at cut-off value 77.

Dual assessment of serum lactate and CRP gave the best discrimination than the use of each of them alone. As it shows an AUC of 0.899 with sensitivity 84.2% and specificity 82.6.

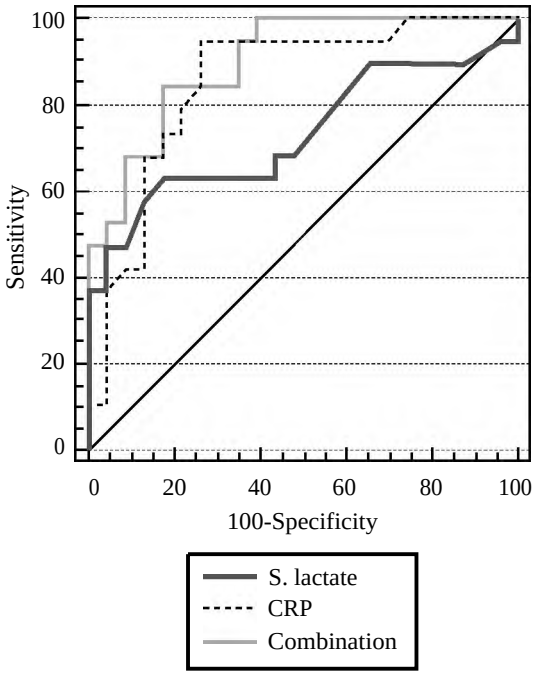

Fig. (1): Receiver operating characteristics (ROC) curve for serum lactate and CPR as prognostic markers for mortality among the studied groups.

Discussion

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is one of the most fatal pandemics which is a multisystem disease caused by incorporation of immunological, inflammatory and coagulative cascades. The clinical presentation of COVID-19 ranges from asymptomatic to critical pneumonia, acute respiratory distress syndrome (ARDS) and even death **[1,2]**. Several studies have shown increased level of pro-inflammatory cytokines in serum of COVID-19 patients.However, the role of inflammatory markers in assessment the severity of COVID-19 is still controversial **[1]**. In this study we have investigated the role of serum lactate and CRP for predicting outcome in covid-19 patients. The present study involved 42 patients that were recruited from ICU isolation partition They were divided into 2 groups; Group 1 (survived) and Group 2 (non-survived).

Non survived patients were older than survived group although this difference was non-significant. The age has important implication in prognosis as aging is usually accompanied with weaker immunity. Most elderly patients already have comorbidities that can result in very high risk of severe disease and death. Non-survived patients usually have more co-morbidities especially IHD and cancer in comparison with survived patients. In match with our study, El-Shabrawy et al., [5] found that severe non-survived patients were older than non-sever cases. Also Li et al., [3] reported that advanced age and underlying cardiac disease were associated with severity. The rate of death is 570 times higher in those who are 85 years and older as approved in the study done by Nabavi et al., [6].

Respiratory acidosis was obvious in non-survived group than survived one (7.32 ±0.10) (7.42±0.09) respectively. We explained that by cytokine storm that resulting in lung injury, respiratory failure and death. The study done byNabavi et al., [6] found that ph. was significantly low in critically ill patients in comparison to sever group. Acidosis can occur in covid-19 patients as a result of respiratory or metabolic acidosis.

In our study po2 was decreased in non-survived group (60.63± 10.84) than survived (61.39 ± 10.82) with non-statistically significant difference between both groups. however,Nabavi et al., [6] 2021 found that O2 saturation was independent predictors of severe/critical COVID-19. ROC curves showed sensitivity of 100% and a specificity of 90.3%.

TLC at time of admission was lower in survived group 8.8 (4.2-13) than non-survived one 14.3 (5-20) although it was non-significant. The study done by selim [10] in Patients with COVID-19 pneumonia may have normal (4-11 x 10^9/L), low, or high leukocyte count. He approved that TLC help in assessment of the progression of the disease and help in doing treatment strategy decision. Absolute lymphopenia which is a typical characteristic of COVID patients was detected in both groups however no significant difference between survived (0.7-2) and non-survived (0.8-3). Many studies correlate with our finding Anurag et al., [7] studied the relation of TLC and its differential count to severity of COVID in 148 patients and found Increased total TLC and lymphopenia were strongly associated with severe illness in comparison with mild and moderate groups. Meta-analysis done by Ji et al., [9] to investigate the association between TLC and lymphopenia in sever COVID patients reported significant higher TLC and marked lymphopenia in those who died during the follow-up than in those who survived. lymphocytopenia (lymphocyte count <1.5 x 10^9/L) were present in severe cases of COVID-19 pneumonia and were associated with bad prognosis in the study done by selim which correlate with our results However he found also that Lymphocytopenia is a reliable indicator of early SARS CoV-2 infection and may be helpful in assessment of disease progression along the course of COVID-19 pneumonia

In this study we estimated the increased blood lactate concentration in sever COVID patients which was significantly higher in non-survived 4 (2-6.2) mmol/L than survived. 2 (1.6-3.4) mmol/L. Serum lactate was measured in the ICU to assess disease severity and predict morbidity and mortality. In study of Vassiliou et al., [11] 122 patients with confirmed COVID-19 infection were included in this study. Of these, 45 patients (37%) required treatment in the ICU with follow-up for 28 days and found that Lactate at 1.85mmol/L represent a sensitivity of 64% and a specificity of 79.4%.

Tissue hypoperfusion usually associated with Increased serum Lactate levels. It has been shown to be interrelated with increased mortality. Serum lactate levels above 4mmol/L were associated with a survival of only 11 % in critically ill patients if this elevation persist for more than 24 hours [12].

Covid-19 pandemic 2020 may further highlight lactic acidosis as one of many markers that may indicate intensive care admission or prognosis in disease.

In our study CRP has been found as an essential marker that changes in severe patients with COVID-19. CRP was a highly statistically significant difference between both groups (p-value <0.01) as it was significantly increased in non-survived 112 (95-154) group than survived one 55 (40-89) as shown in Table (3).

As Inflammation stimulate the liver to produce many acute-phase reactants. One of such important reactants is C-reactive protein (CRP), which can be used as biomarker in many conditions as in the presence of infection or cardiovascular disease [13]. It has been reported that in severe COVID-19 patients, CRP levels may raise before any findings can be observed on CT and thus CRP can be used to detect severe cases at an early stage [14].

The cause of elevation of CRP in patients with COVID-19 may be due to the overproduction of inflammatory cytokines [15]. Those cytokines fight against the microbes but when the immune system

becomes hyperactive, it causes damage of lung tissue **[16]**.

The study done by Chen et al., **[13]** found that elevated CRP level were observed up to 86% in severe COVID-19 patients which correlate with our results. Also, the study done by Wang et al **[16]** approved that there is increase in the risk of developing severe events in patients with COVID-19 by 5% for every one-unit increase in CRP concentration.

A study done by Chen et al., **[13]** reported that patients with mild symptoms have CRP concentration of 18.8 while patients with more severe symptoms had on average high CRP concentration of 39.4mg/L.

A study done by Guane et al., **[18]** found that patients with low oxygen saturation (SpO2 ≤90%) had significantly higher levels of CRP (median 76.5mg/L) in comparison to patients with high oxygen saturation (SpO2>90%) had a lower level of CRP (median 12.7mg/L), as mentioned by Xie et al., **[19]** in his study on 140 COVID-19 patients indicating that more severe patients with lung damage have more elevated levels of CRP, so it may be an important marker in evaluating a patient's conditions in combination with other clinical findings.

Conclusion serum lactate and CRP both of them are useful marker in early differentiation of severity in patients hospitalized due to COVID-19. Dual assessment of serum lactate and CRP gave the best discrimination than the use of each of them alone.

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دور اللاكتات وبروتين سى التفاعلى فى التنبأ بما سيحدث لحالات الكورونا

بدأ انتشار فيروس كورونا من واهان فى الصين فى ديسمبر ٢٠١٩ إلى جميع أنحاء العالم وقد وجد أن التشخيص السريع للحالات المتدهورة قد يفيد فى بداية العلاج الصحيح المبكر وقد يفيد فى بداية العلاج الصحيح المبكر وقد يؤدى إلى تقليل حالات الوفيات.

الهدف من البحث: هو دراسة دور كل من اللاكتات وبروتين سى التفاعلى فى التنبؤ بما يحدث لحالات كورونا المحجوزة بالمستشفى.

المرضى والطرق: فى هذا البحث تم إجراءه على ٤٢ مريض تم تقسيمهم إلى أحياء ووفيات وتم حساب دلالات الإلتهاب مثل عدد كرات الدم البيضاء والخلايا الليمفاوية وبروتين سى وحمض الاكتات.

النتائج: المرضى المتوفين كانوا يعانون من زيادة بحموضة الدم وارتفاع نسبة الاكتات وبروتين سى التفاعلى هذا ما اثبته منحنى الروك.

الاستنتاج: حمض اللاكتات وبروتين سى هى دلالات مهمة للتبؤ بدرجة خطورة حالات الكورونا المحجوزة بالمستشفى ودراسة هاتان الدلالتان سويا يعد تقييم جيد للحالات.