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Original article

Association between presepsin, C-reactive protein (CRP), lactate dehydrogenase (LDH) and prognosis of COVID-19

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ABSTRACT

Background: Different biomarkers are used in prognostic evaluation of COVID-19 patients. Presepsin (PSN) is a soluble CD14 subtype that was proposed as a novel biomarker in patients with sepsis as inflammatory cytokine. The purpose of this study was to determine the association of PSN, C-reactive protein (CRP) and Lactate dehydrogenase (LDH) with the outcome of COVID-19 patients. **Material and methods:** A total of 125 severe/critical COVID-19 patients were involved in this work divided in two groups based on survival, dead group 62 patients and live group 63 patients. Patients were determined as severe cases according to the guidelines released by National Health World depending on SpO2 percentage. The inflammatory cytokine (PSN) was detected by the ELISA technique. **Results:** PSN showed no statistical differences between lived median (IQR) 296.4 (227.5- 324.2) pg/ml and dead patients 258.4 (250.9- 301.1) pg/ml (***p*** = 0.51). LDH increased significantly in dead 771 (625- 957) U/L compared to lived patients 259 (198- 381) U/L (***p*** <0.001). CRP elevated in dead patients 57 (91.9%) compared to live patients 50 (79. 4%) significantly (***p*** = 0.04). Negative significant correlation was observed between CRP and LDH (r= -0.21, ***p*** = 0.019) as well as CRP revealed negative significant correlation with PSN (r= -0.21, P= 0.018). **Conclusions:** PSN revealed no significant differences between dead and lived patients with COVID-19. The sensitivity of LDH was 93%, the specificity was 85%, and the cut point was 468 IU/ml that was significantly elevated in dead patents (***p*** < 0.001). CRP significantly increased in dead patients (***p*** = 0.04).

Introduction

Coronavirus disease 2019 (COVID-19),occured due to contagion with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that stated as a pandemic lately, majority of cases are self-limiting; nonetheless, it can proceed to a severe form with a high death rate at any time [1,2].

The SARS-CoV flare-ups in both 2002 and 2003, as well as the Middle East Respiratory Syndrome-Coronavirus (MERS) outbreak in 2012, showed the scope for newly developing coronaviruses to be transmitted from animal to the human and individual to another [3]. HCoV229E, HCoV-OC43, MERS-CoV, SARS-CoV, HKU1, and SARS-CoV-2 are among the seven human coronaviruses (HCoVs) presently known [4,5].

Recently, the soluble CD14 subtype PSN was suggested as a new biomarker in patients with sepsis. It participates in the initial stages of the septic process, and studies have shown its significance in risk stratifying patients with sepsis and its ability to distinguish between those with sepsis and those progressing to septic shock [6].

PSN is released into the circulation when an infectious pathogen activates monocytes. PSN levels therefore continue to increase throughout the

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early stages of sepsis. A dose-response mechanism of the host-pathogen interaction, which occurs in the early stages of pathogen identification and persists for a number of days depending on the severity of the disease, has been hypothesized to be the origin of the increase in PSN. There have not been yet enough studies done to fully understand and examine the role of PSN in COVID-19 patients [7].

According to reports, PSN is a new biomarker for sepsis. Numerous studies have demonstrated that PSN is helpful for diagnosing sepsis and may also be able to predict the severity and mortality of the condition. Additionally, higher PSN may serve as an important biomarker in the evaluation of COVID-19 patients, according to recent reports [8,9].

According to reports, PSN is a new biomarker for sepsis. Numerous studies have demonstrated that PSP is helpful for diagnosing sepsis as well as perhaps predicting the severity and mortality of the condition. Additionally, higher PSN may serve as a biomarker in the prognostic evaluation of patients with COVID-19 [10].

LDH is a terminating enzyme used in the metabolic pathway of anaerobic glycolysis, creates lactate as the last product from glucose. The production of lactate is necessary for the metabolism of glucose when there is not enough oxygen available. For a number of disorders, including as ARDS, severe COVID-19, and cancer patients, the LDH is utilized to forecast death. Since lactate functions as an energy source, a signaling molecule, and a pH regulator; it is crucial to human physiology in its normal state [11].

The aim of the current study was to detect the relation of PSP with the outcome of COVID- 19 as well as other inflammatory biomarkers such as LDH and CRP.

Material and methods

A total of 125 severe COVID-19 patients were recruited in this study; they were all hospitalized to the COVID-19 wards of Al-Sadeq Hospital and Marjan Medical City from 3/2/2022 to 24/6/2022. They were between the ages of 16 and 90. Females were more prevalent than males. Each patient in this investigation had reverse transcriptase-polymerase chain reaction (RT-PCR) results that were positive for SARS-CoV-2, which supported the diagnosis of COVID-19. Patients were divided to two groups based on survive; 62 dead group and 63 live group. Based on the SpO2 percentage, patients were classified as severe or critical (90%) [12].

Each patient, whose PSN level was measured, had blood and serum samples taken. BT LAB Company ELISA kits were used to detect PSN level. A Biotek EL800 automated immunoassay analyzer was used to measure LDH (BioTek, USA). CRP was detected by qualitative slide method.

Included patients in this study were those admitted to hospital due to severe acute respiratory syndrome which was confirmed by RT-PCR with decreased SpO2 percentage. Excluded criteria included patients with autoimmune disease and cancer as well as patients with negative result of RT-PCR.

The Babylon Health Directorate approved the moral position. Before taking the sample, permission from the patient and his relatives was sought. In addition to sampling, safety and health precautions were implemented. Consent to participate was taken from all participants. The approval number and date were (19814 in 1/2/2022).

Results

Data were put into SPSS for Windows version 26 for statistical analysis (GraphPad Software, San Diego, California, USA). The outcomes were presented as median (25th–75th interquartile range, IQR). The Mann–Whitney U test was used to compare two groups. Chi- square was used for non- parametric variables. $\boldsymbol{p}$ value < 0.05 was taken into account to denote statistical significance. Additionally, Spearman's correlation test used to explain the connection between pro-inflammatory cytokine serum levels (PSN), LDH and CRP.

In the current study, the median of age was 75 (62-85) years. Sex distribution was 44.8% males and 55.2% females. The median of presepsin in patients was 261.49 (244- 324.26) ng/ml while the median for LDH 504 (257-788) IU/L **(Table 1)**.

Presepsin showed no statistical differences between lived patients median (IQR) 296.4 (227.5-324.2) pg/ml and dead patients 258.4 (250.9- 301.1) pg/ml ($\boldsymbol{p}$= 0.51). LDH increased significantly in dead 771 (625- 957) U/L compared to lived patients 259 (198- 381) U/L (P< 0.001) **(Table 2)**.

In a total of 125 patients, CRP was positive in 107 (85.6%) and negative in 18 (14.4%). From 63 lived patients, 50 (79. 4%) were CRP positive while 13 (20.6%) give negative result for CRP. On the other hand, from total of 62 dead patients, 57

(91.9%) give positive result, whereas just 5 (8.1%) gave negative result for CRP (***p***= 0.04) **(Table 1)**.

The ROC or area under the curve (AUC) showed that the sensitivity of LDH was 93%, the specificity was 85%, and the cut point was 468. **(Table 3)** and **(Figure 1)**.

Negative significant correlation was observed between CRP and LDH (r= -0.21, ***p***= 0.019) as well as CRP revealed negative significant correlation with presepsin (r= -0.21, ***p***= 0.018). No significant correlation was noted between LDH and presepsin (***p***= 0.1) **(Table 4)**.

Table 1. Demographic study of patients with COVID-19

Variables (Units)	Patients (N= 125) Median (IQR) or (No. %)
Age (years)	75 (62-85)
Gender Males Females	 56(44.8%) 69 (55.2%)
SpO_2 (>94)	82 (78-88)
CT scan (Negative)	45 (20-67)
Presepsin (ng/ml)	261.49 (244- 324.26)
CRP	107 (85.6%)
Lactate dehydrogenase (IU/L)	504 (257-788)

Table 2. Distribution of variables according to status of patients (Live or Dead)

Variables	Status of patients	Number	Median (IQR) Or NO (%)	***p*** value
Presepsin (pg/ml)	Live	63	296.4 (227.5- 324.2)	0.51 #
	Dead	62	258.4 (250.9- 301.1)	
LDH (U/L)	Live	63	259 (198- 381)	< 0.001 #
	Dead	62	771 (625- 957)	
CRP	Live	63	50 (79.4%)	0.04 ¥
	Dead	62	57 (91.9%)	

Lactate dehydrogenase (LDH); C- reactive protein (CRP); Mann–Whitney U test (#); Chi- square (¥)

Table 3. Sensitivity, specificity, and cut point for different inflammatory variables

Variables	AUC	Std. Error	Sig	Lower bond	Upper bond	Cut point	Sens.	Spec.
LDH	0.925	0.025	<0.001	0.877	0.973	468.00	0.935	0.857
Presepsin	0.533	0.053	0.51	0.429	0.638	292.36	0.508	0.758

Table 4. Correlation between different parameters

Variables		CRP	Presepsin
LDH	Correlation Coefficient	-0.210-*	-0.118-
	Sig. (2-tailed)	0.019	0.190
CRP	Correlation Coefficient		-0.211-*
	Sig. (2-tailed)	.	0.018

Figure 1. Area under the curve for LDH

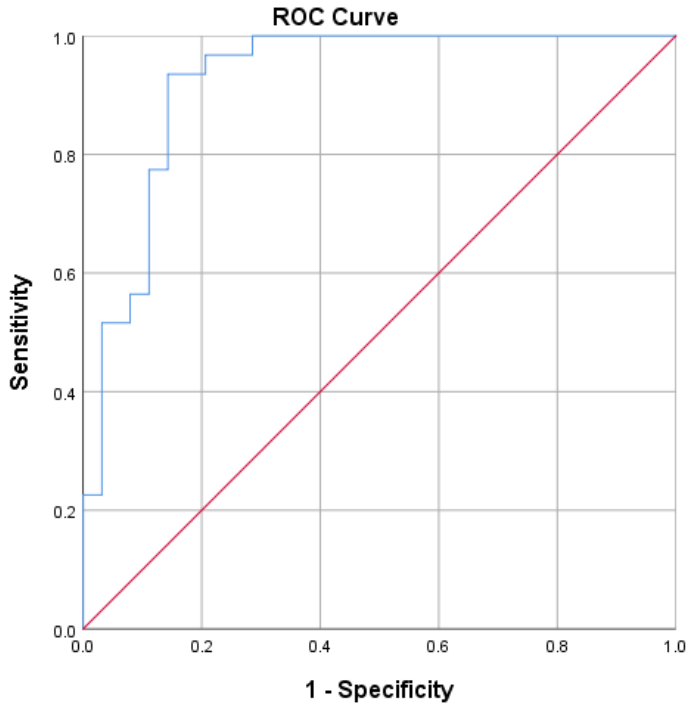
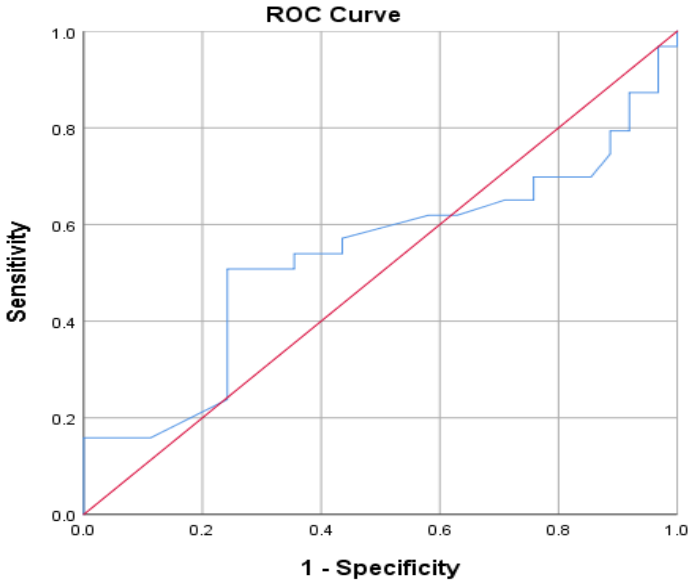


Figure 2. Area under the curve for presepsin



Discussion

Sometimes, the immune system's reaction to a viral infection might be more destructive than the virus itself [13,14]. In order to manage COVID-19, immunopathogenesis must also be taken into account. Presepsin has only been the subject of a small number of investigations; therefore its role in preventing viral infection is still not fully known [15].

To more effectively use the limited resources available, it is essential to be able to identify which patients would have a higher chance of dying. In order to do this, a number of inflammatory markers were investigated to detect how well they can affect mortality outcomes [16].

The current study found that presepsin showed no statistical differences between lived and dead patients (***p***= 0.51). This result conflicts with another study's findings that mentioned the level of presepsin was considerably higher in the non-survivor group compared to the survivor group (***p*** = 0.001) and in ICU patients compared to non-ICU patients (***p***= 0.001). Additionally, it showed that elevated levels were linked to longer hospital stays. In-hospital mortality was shown to be linked to concentrations over 775 pg/mL (sensitivity 73%), specificity 80%) [17]. All patients participated in this study were severe/ critical patients with high rate of mortality, so pro-inflammatory cytokines including PSN might have decreased with time and anti-inflammatory parameters might have increased.

The PSN prognostic value for predicting 30-day death in COVID-19 patients was also investigated in this study. In COVID-19 patients that were hospitalized, PSN was performed comparably in terms of predicting 30-day death [18]. PSN has demonstrated adequate performance in predicting the worsening of severity in COVID-19, which can help doctors to identify high-risk patients and choose treatment plans early for the best use of available resources [19].

Another research with 85 patients who had COVID-19 infection found that the mean PSN levels in the patient group was considerably higher than in the control group (1.4830.147 ng/mL versus 0.8730.103 ng/mL). PSN levels showed a high association with procalcitonin levels and creatinine levels and a slight positive link with CRP levels. 53 patients in the patient group have healed and been released, while 7 people have passed away. The presepsin levels in the patient group that recovered and dying patients' group did not differ significantly [20].

In the current study, the ROC or AUC showed that the sensitivity of LDH was 93% and the specificity was 85%. Cut point for LDH was 468 IU/ml. CRP was elevated in dead patients 57 (91.9%) compared to live patients 50 (79. 4%) significantly (***p***= 0.04).

Ruan et al. who found greater levels of CRP and serum ferritin in patients who had been discharged; hypothesized that virus-activated cytokine storm syndrome may be the cause of COVID-19 mortality in research on the clinical predictors of COVID-19 mortality [21].

These findings compatible with another study that mentioned the cutoff values for the parameters were 33.55 mg/L for CRP, 263.5 U/L for LDH, each with high sensitivity and specificity [22].

A noteworthy inflammatory state is typically seen in severe COVID-19, as seen by elevated blood CRP and LDH levels [23]. The development of ARDS, myocardial damage, and mortality were also linked to increased CRP levels in COVID-19 patients [24]. According to a meta-analysis, individuals with COVID-19 were more likely to die, develop ARDS, and require ICU care when their inflammatory levels increased in their serum [25]. Other explanations for the increases in these inflammatory indicators include bacterial infections and subsequent viral infections. Thus, it may be advised to use these indicators to track the development and improvement of COVID-19 patients [26-28].

The main limitation in the current work was lack of genotyping study as single nucleotide polymorphisms for genes encode PSN, LDH, and CRP. Sample size was small and may not reflect the total population. Estimation of the anti-inflammatory parameters may be useful as well as PSN detection.

Conclusion

Presepsin showed no significant differences between dead and lived patients with COVID-19 (***p***= 51). CRP significantly increased in dead patients (***p***= 0.04). LDH level above 468 U/L was significantly combined with mortality (specificity 85%, sensitivity 93%). Elevated LDH and CRP levels are signs of poor outcomes and should serve as a warning to the doctors when deciding whether to monitor critical care patients or initiate further therapies.

Conflict of interest

Not declared.

Funding

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