ORIGINAL ARTICLE

C-reactive protein-to-lymphocyte ratio is a reliable marker in patients with COVID-19 infection: the CLEAR COVID study

La proporción de proteína C reactiva a linfocitoE es un marcador confiable en pacientes con infección por COVID-19; el estudio CLEAR COVID

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Abstract

Objective: *COVID-19 infection is characterized with elevation of inflammatory markers in bloodstream. A novel inflammatory marker, C-reactive protein (CRP)-to-lymphocyte ratio (CLR), is suggested to be associated with inflammation. We aimed to compare the CLR values of the deceased COVID-19 patients to the CLR of survived subjects.* **Materials and Methods:** *The patients with COVID-19 whom presented to outpatient or inpatient clinics of AbantIzzet Baysal University Hospital were enrolled to the present retrospective study. Subjects were grouped as either deceased or survived. CLR values of the groups were compared.* **Results:** *Study cohort was consisted of 568 subjects in deceased and 4753 patients in survived group. Median CLR of the deceased and survived groups were 90 (0.2-1679)% and 11 (0.2-1062)%, respectively (p < 0.001). The sensitivity (75%) and specificity (70%) of CLR (> 23.4% level) in detecting mortality were higher than those of CRP and ferritin (AUC: 0.80, p < 0.001, 95% CI: 0.78-0.82).* **Conclusion:** *We suggest that elevated CLR levels in COVID-19 patients on admission should alert physicians for poor outcome.*

Keywords: *COVID-19. Mortality. Inflammation. C-reactive protein-to-lymphocyte ratio.*

Resumen

Objetivo: *La infección por Covid-19 se caracteriza por elevación de marcadores inflamatorios en el torrente sanguíneo. Se sugiere que un nuevo marcador inflamatorio, la proporción de C-reactive protein (CRP) a linfocitos (CLR), está asociado con la inflamación. Nuestro objetivo fue comparar los valores de CLR de los pacientes fallecidos con Covid-19 con el CLR de los sujetos sobrevivientes.* **Materiales y Métodos:** *Los pacientes con Covid-19 que se presentaron en clínicas ambulatorias o de hospitalización del Hospital Universitario Abant Izzet Baysal se inscribieron en el presente estudio retrospectivo. Los sujetos se agruparon como fallecidos o sobrevivientes. Se compararon los valores de CLR de los grupos.* **Resultados:** *La cohorte del estudio estuvo compuesta por 568 sujetos en el grupo fallecido y 4753 pacientes en el grupo sobreviviente. La mediana de CLR de los grupos fallecidos y sobrevivientes fue 90 (0.2-1679)% y 11 (0.2-1062)%, respectivamente (p < 0.001). La sensibilidad (75%) y la especificidad (70%) de CLR (nivel > 23.4%) en la detección de mortalidad fueron superiores a las de CRP y ferritina (AUC: 0.80, p < 0.001, IC 95%: 0,78-0.82).* **Conclusión:** *Sugerimos que los niveles elevados de CLR en pacientes con Covid-19 al ingreso deberían alertar a los médicos sobre un resultado deficiente.*

Palabras clave: *Covid-19. Mortalidad. Inflamación. Proporción de proteína C reactiva a linfocitos.*

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Introduction

The end of 2019 and the beginning of 2020 witnessed the declaration of a new pandemic in the world. At the beginning of the pandemic, we did not foresee that our lives would be so affected by COVID-19. COVID-19 has caused many deaths, morbidities, and economic hardships in the nearly 2 years since the first case emerged.

COVID-19 usually begin with common flu symptoms[1], however, may cause dyspnea and other serious signs and symptoms related to many other organ systems. Despite it can cause asymptomatic infection, serious disease or even death may also occur related to COVID-19. Thus, several prognostic and easy to assess markers have been proposed to be related with the severity and outcome of the disease. These include neutrophil/lymphocyte ratio[2], platelet/lymphocyte ratio[3], mean platelet volume[4], ferritin[5], C-reactive protein (CRP)[6], and lactate dehydrogenase[7]. Unfortunately, none of these laboratory markers were as effective as desired in predicting serious morbidity and mortality. Therefore, there is a need for a marker that can effectively predict the course and prognosis of COVID-19 infection.

A novel inflammatory marker, CRP-to-lymphocyte ratio (CLR), has been studied in various conditions in recent works in the literature. Authors suggested it as a promising predictor of various types of cancers, which are associated with sustained inflammation[8,9]. COVID-19 infection is also characterized with prominent inflammatory burden. Therefore, we hypothesized that CLR could be associated with mortality in these population.

To investigate this hypothesis, in present study, we aimed to compare the CLR values of the patients who died due to COVID-19 with the CLR values of the patients who survived.

Materials and methods

Design, setting, and population

Patients with COVID-19 infection whom presented to outpatient and inpatient internal medicine clinics of our institution between April 2020 and October 2021 were enrolled to the present retrospective study after study protocol was approved by the Institutional Ethics Committee (approval no: 2021/272). Subjects whom become COVID-19-positive while already hospitalized for another reason were not included in the study. Subjects younger than 18 years old were also excluded from the study. Study population were divided into two groups according to the outcome, deceased patients' group, and survived patients' group.

Anthropometric and laboratory analyses

Day of hospital stay, treatment duration in intensive care unit (if any), presence or absence of comorbidities such as diabetes mellitus, hypertension, coronary heart disease, and congestive heart failure were recorded. Age, gender, CRP, hemogram indices (white blood cell count [WBC], lymphocyte count [lym], hemoglobin [Hb], Hematocrit [Hct], platelet count [PLT]), ferritin, lactate dehydrogenase (LDH), d-dimer, and serum albumin levels were obtained from institutional database and patients' files. All laboratory parameters were the initial values on hospital admission. A CLR was simply calculated by division of CRP by lym. Lymphocyte count in microliter, not lymphocyte percentage was used in calculation of CLR. Data of the deceased and survived patients were compared.

Statistical analyses

Statistical analyses were conducted with a statistics software (SPSS 18.0 for Windows, IBM Co., Armonk, NY, USA). Normality analysis of the variables were done with Kolmogorov–Smirnov test and additionally supported by the histogram and skewness–kurtosis coefficients of ± 1. Data that fit into normal distribution were expressed as means and standard deviations and compared by independent samples t-test. Skewed data were compared with Mann–Whitney U-test and were expressed as median (min-max). Categorical variables were compared with Chi-square test and expressed as numbers and percentages. Pearson's correlation analysis test was used in analysis of correlation between ALR and other study variables. Binary logistic regression analysis was used to determine whether CLR was independent risk factor for mortality by taking into account other variables such as age, days of hospital stay, treatment duration in intensive care unit, gender, CRP, WBC, Plt, ferritin, LDH, d-dimer, and serum albumin levels. The sensitivity and specificity of CLR and other variables in predicting mortality were conducted by receiver operative characteristics (ROC) test. Coordinate points were used to clarify the best cutoff points CLR, ferritin, and CRP

in determination of their sensitivity and specificity in predicting mortality. Statistical significance was considered when p value was below 0.05 range.

Results

Study cohort was consisted of 5321 patients; 568 subjects in deceased and 4753 patients in survived group. Median ages of the survived and deceased groups were 50 (18-97) years and 75 (22-98) years, respectively. Deceased subjects were significantly older than the survived patients (p < 0.001). Survived group was consisted of 2696 (57%) women and 2057 (43%) men, while deceased group was consisted of 250 (44%) women and 318 (56%) men. The rate of men in deceased group was significantly higher than the rate of women compared to the survived group (p < 0.001).

The rates of intensive care admission (p < 0.001) and comorbidity (p < 0.001) were higher in deceased group compared to the survived patients.

Blood Hb (p = 0.4) and Htc (p = 0.1) levels of the deceased and survived groups were similar. However, day of hospital stay (p < 0.001) and treatment duration in intensive care unit (p < 0.001) were significantly longer in deceased group compared to the survived subjects. Similarly, CRP (p < 0.001), LDH (p < 0.001), d-dimer (p < 0.001), ferritin (p < 0.001), and WBC (p < 0.001) levels of the deceased subjects were significantly increased compared to those of survived patients. On the other hand, serum albumin (p < 0.001), lymphocyte count (p < 0.001), and platelet count (p < 0.001) of the deceased group were significantly decreased compared to those in survived group. Table 1 shows data of the deceased and survived groups.

Median CLR of the deceased and survived groups were 90 (0.2-1679)% and 11 (0.2-1062)%, respectively (p < 0.001).

The CLR level was significantly and positively correlated with age (r = 0.32, p < 0.001), LDH (r = 0.41, p < 0.001), d-dimer (r = 0.15, p < 0.001), ferritin (r = 0.37, p < 0.001), and WBC (r = 0.12, p < 0.001) levels. In contrast, CLR was inversely correlated with albumin (r = −0.39, p < 0.001) and PLT (r = −0.12, p < 0.001).

Binary logistic regression analysis showed that CLR was an independent risk factor for mortality in COVID-19 patients by taking into account age, days of hospital stay, treatment duration in intensive care unit, gender, CRP, WBC, Plt, ferritin, LDH, d-dimer, and serum albumin levels (p < 0.001, OR: 1.3, 95% CI: 1.01-1.4).

Table 1. Data of the deceased and survived groups

	Survived	Deceased	p
	X^2		
Gender			
Women (n, %)	2696 (57%)	250 (44%)	< 0.001
Men (n, %)	2057 (43%)	318 (56%)	
Comorbidity			
Present (n, %)	1945 (41%)	551 (97%)	< 0.001
Absent (n, %)	2808 (59%)	17 (3%)	
ICU admission			
Present (n, %)	493 (10%)	525 (92%)	< 0.001
Absent (n, %)	4260 (90%)	43 (8%)	
	Median (min.-max.)		
Age (years)	50 (18-97)	75 (22-98)	< 0.001
Hospitalization duration (days)	1 (0-290)	16 (1-70)	< 0.001
Duration in ICU (days)	0 (0-58)	8 (0-70)	< 0.001
CRP (mg/L)	14.9 (0.6-287)	79 (0.5-320)	< 0.001
Albumin (g/dL)	4.2 (1.8-5.7)	2,9 (1.5-4.8)	< 0.001
LDH (U/L)	252 (40-1884)	357 (126-1945)	< 0.001
D-dimer (ng/mL)	0.4 (0.1-80)	0.9 (0.1-58)	< 0.001
Ferritin (mcg/L)	103 (1-4275)	305 (2.8-1882)	< 0.001
WBC (k/mm^3)	6 (2.3-36)	7.2 (1.1-34)	< 0.001
Lym (k/mm^3)	1.4 (0.2-22)	0.9 (0.1-11)	< 0.001
Plt (k/mm^3)	239 (2-1229)	210 (8-598)	< 0.001
CLR (%)	11 (0.2-1062)	90 (0.2-1679)	< 0.001
	Mean ± SD		
Hb (g/dL)	13.5 ± 1,8	13.7 ± 1.9	0.4
Htc (%)	40.5 ± 5	41.3 ± 6	0.1

ICU: intensive care unit; CRP: C-reactive protein; CLR: c-reactive protein-to-lymphocyte ratio; WBC: white blood cell; lym: lymphocyte count; Hb: hemoglobin, Hct: hematocrit, PLT: platelet count, LDH: lactate dehydrogenase.

The sensitivity and specificity of CRP, ferritin and CLR in detecting mortality were studied by ROC analysis test. The sensitivity and specificity of CRP (> 31.9 mg/L level) were 72% and64%, respectively (AUC: 0.77, p < 0.001, 95% CI: 0.75-0.79). Sensitivity and specificity of ferritin (>150.9 mcg/L level) in detecting mortality were 71% and 60%, respectively (AUC: 0.75, p < 0.001, 95% CI: 0.73-0.77). The sensitivity (75%) and specificity (70%) of CLR (> 23.4% level) in detecting mortality were higher than those of CRP and ferritin (AUC: 0.80, p < 0.001, 95% CI: 0.78-0.82). Figure 1 shows the ROC curves of CRP, ferritin, and CLR in detecting mortality in study cohort.

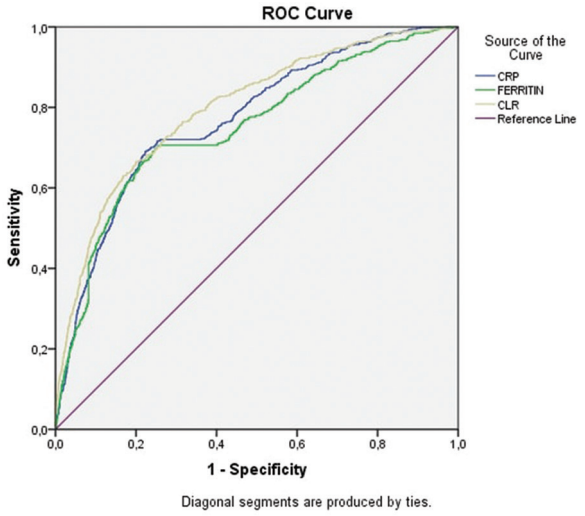

Figure 1. *Receiver operative characteristics curves of C-reactive protein (CRP), ferritin, and CRPs-to-lymphocyte ratio in detecting mortality.*

Discussion

The present study showed first time in literature that elevated CLR levels could be associated with the prognosis of COVID-19 patients. We also reported moderate and strong correlations between CLR and other laboratory indices of COVID-19 infection. Finally, interesting results of the present work implied that CLR has better sensitivity and specificity in predicting mortality compared to CRP and ferritin, other possible prognostic markers in this population.

Inflammation is a part of the underlying pathological mechanism of COVID-19 infection. Viral entry to human cell induces an inflammatory response which enhanced by inadequate viral clearance in advanced phase of the disease[10-12]. Disease may even cause a cytokine storm which increases the morbidity and mortality in these subjects[13]. The widely used inflammatory marker, CRP, has been found to be increased in COVID-19 patients and associated with accurate diagnosis[14]. Therefore, it is not surprising those inflammatory markers to be increased in serum of the COVID-19 patients. Elevated CRP, ferritin, LDH, d-dimer, and WBC levels which reported in present study were in accordance with the literature data. Moreover, we showed that CLR, another novel derived inflammatory marker, could serve as a well predictor of inflammatory burden in COVID-19 subjects with poor prognosis.

Studies in the literature have shown the association between CLR and inflammatory conditions. Fan et al. studied the newly discovered inflammatory indicator, CLR, as a possible prognostic biomarker in pancreatic cancer and found that CLR was better than any other prognostic factors in predicting survival in patients with pancreas cancer[8]. Subsequently, their findings were supported by another work[15]. In a recent study, authors investigated whether CLR has prognostic role in patients that received esophagogastric resection for cancer and reported that CLR was a useful predictor of major morbidity after esophagogastric resection surgery[9]. Authors studied pre-operative CLR values of the subjects with oral squamous cell carcinoma and concluded that CLR was associated with better prognostic performance compared to other inflammatory markers and elevated CLR levels indicated poor overall and disease-free survival in this population[16]. Similarly, Meng et al. investigated CLR in patients with colorectal cancer and reported that patients with high CLR had shorter overall survival than those with low CLR levels[17]. Mungan et al. report confirmed the results of Meng et al. study, subsequently[18]. Moreover, prognostic value of elevated CLR has been also shown in patients with lung cancer[19], osteosarcoma[20], and cholangiocarcinoma[21]. It is a fact that malignant conditions are associated with increased inflammatory burden[22], as seen in patients with COVID-19 infection. Therefore, increased CLR levels in COVID-19 patients with worse prognosis which reported in present study are a finding that consisted with the literature knowledge.

Several studies reported the diagnostic and predictive value of CLR in conditions other than cancer. Authors studied reverse proportion of CRP and lym and found that this proportion could be a useful marker for estimating intestinal ischemia in subjects with incarcerated hernia[23]. In addition, high CRP and low lymphocyte count, which means elevated CLR, have been reported in patients with heart failure[24]. Both ischemia and heart failure are associated with increased inflammation, as seen in COVID-19 infection. Ischemia and heart failure are associated with reduced blood supply of the tissues and cause an increase in inflammatory burden consequently. Therefore, elevated CLR in deceased patients compared to survived subjects in COVID-19 population which reported in present study can be explained with this phenomenon.

To the best of our knowledge, CLR has not been compared previously in the literature between deceased and survived COVID-19 patients. However, several studies reported elevated CRP and low lymphocyte count levels, which could mean increased

CLR, in COVID-19 subjects with poor prognosis[25-28]. In this study, we combined the CRP and lymphocyte count, as CLR and showed their association with poor prognosis in COVID-19 patients. The best cutoff value for CRP in predicting mortality in the present study was lower than similar works in the literature, that is, Sadeghi et al. study[29].{Sadeghi-Haddad-Zavareh, 2021 #39} There are some possible reasons for this difference. Initially, all inpatient and outpatient COVID-19 patients were enrolled to the present study. Outpatients are mostly survived and they also tend to have lower CRP levels. Second, Sadeghi et al. compared mild and severe COVID-19 subjects, while we compared CRP of survived and deceased patients. Finally, more than 5000 subjects were enrolled to the present study, while over 400 patients made the study population in Sadeghi et al. work. These points could explain the difference in CRP levels between present study and other published works.

Single-center nature of the present study and the retrospective design of the work are two main limitations of the present study. However, this is the first work in the literature pointed out significant association between elevated CLR and mortality in COVID-19 population.

Conclusion

We suggest that elevated CLR levels in COVID-19 patients on admission should alert physicians for poor outcome. More cautious and attentive medical care may be required in these subjects.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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