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Original Article

COVID-19 : Correlation Between CRP and LDH to Disease Severity and Mortality in Hospitalized COVID-19 Patients

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Abstrak

Background : COVID19 is a newly emerging disease and considered an emergency health problem, worldwide. It has a wide range of clinical features, from mild fever to severe respiratory failure that leads to a higher mortality rate. Previous studies state that CRP has a very strong positive correlation with the diameter of the lung lesion, and in intensive care patients had a higher level of LDH. This study aims to determine the correlation between CRP, LDH and disease severity and mortality in hospitalized COVID-19 patients.
Methods : We conducted a retrospective cohort, a single-center study including 69 laboratory-confirmed patients in our hospital in Malang City, Indonesia from April – June 2020.
Results : Subjects consisted of 26 patients (37.7%) in the mild-moderate group and 43 patients in severe group (62.3%). Statistical analysis showed CRP and LDH associated with disease severity (p=0.011 and p<0.001). Analysis of CRP and LDH in survivor and non-survivior group showed that CRP and LDH also asscociated with mortality in hospitalized COVID-19 patients (p=0.034 and 0.002). We also evaluate CRP and LDH with degrees of hypoxemia by assessed P/F ratio. Statistical analysis showed that CRP did not correlate with degrees of hypoxemia (p=0.079) but LDH inverse correlate with degrees of hypoxemia (p<0.001, pearson correlation = -0,489).
Conclusion : In our retrospective cohort study demonstrated LDH and CRP can be a crucial indicator to predict severity and mortality for hospitalized COVID-19 patients and LDH may usefull test for predict early identification of patients who become respiratory failure or ARDS.

Keywords : COVID-19, LDH, CRP, P/F Ratio

INTRODUCTION

Corona Virus Disease (COVID-19) is a critical worldwide health problem. The disease stems from a reported case of pneumonia without a clear etiology in Wuhan City, Hubei Province, China on December 31, 2019, which was later identified as a new type of Corona Virus.[1] The virus was later named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[2] Indonesia first reported COVID-19 cases on 2 March 2020 in a number of 2 cases.[3] Dated July 24, 2020, COVID-19 reached 15.012.731 cases globally with 4,1% deaths and in Indonesia reached 93.657 cases with 4.576 deaths (4,9%).[4] The high mortality rate is closely related to the severity of the disease, so early detection of disease severity is one of the keys to reducing mortality.[5,6]

C-reactive protein (CRP) is an acute phase protein synthesized by liver mainly as a reaction to IL-6 and that inflammatory markers can play a role in predicting severity in Community Acquired Pneumonia.[7] As we know pathogenesis of COVID-19 based on a cytokine mediated hyperinflammatory process that developed into cytokine storm. Hyperinflammation biomarkers include CRP, IL-6, Ferritin, D-dimers, LDH, Procalcitonin, lymphopenia and thrombocytopenia.[8] This study aims to determine the correlation between CRP, LDH and disease severity and mortality in hospitalized COVID-19 patients.

MATERIAL AND METHODS

In our retrospective cohort, single-center study, we obtain 69 patients. The inclusion criteria for this study are COVID-19 patient confirmed by real-time Polymerase chain reaction (rt-PCR) or GeneXpert® SARS-CoV-2 rapid molecular testing method. Our patient treaded in PINIERE room ("Penyakit infeksi Emerging dan Re-emerging", Emerging and Re-emerging Infectious Disease) as our isolation ward. All data collected from April June 2020.

The severity of COVID 19 are assessed as follows: (1) Mild severity includes Patients with non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle aches. (2) Moderate severity includes adolescent or adult patients with clinical signs of pneumonia (fever, cough, dyspnea, rapid breathing) and no signs of severe pneumonia. (3) Severe symptoms include adolescent or

TABLE 1
Association baseline demographic variables and disease severity

Variables		Disease Severity		*p-value*
		Mild Moderate (n=26) Mean (Min–Max)	Severe (n=43) Mean (Min–Max)	
Age (Years)	≤ 50	9 (34.61%)	13 (30.23%)	0.705
	> 50	17 (65.39%)	30 (69.77%)	
Sex	Male	11 (15.94%)	27 (%)	0.097
	Female	15 (%)	16 (%)	
Smoking Status	Never	23 (88.46%)	25 (58.14%)	**0.028***
	Ex-smoker	2 (7.69%)	9 (20.93%)	
Current smoker		1 (3.85%)	9 (20.93%)	
WBC (cell/µL)		8144.62 (3900–20930)	10270 (3250–29250)	0.128
Neutrophil (cell/µL)		6261.49 (2117.70–17895.15)	8706.40 (2372.50–27904.50)	**0.032**
Lymphocytes (cell/µL)		1288.56 (304.00–2609.50)	1013.13 (428.00–1850.00)	0,074
Monocytes (cell/µL)		540.92 (171.00–1254.00)	540.71 (152.40–1908.90)	0.544
Platelet (cell/µL)		271653.85 (142000–766000)	249837.21 (118000–471000)	0.901
Hb (g/dL)		12.98 (8.40–17.60)	13.87 (10.80–17.50)	0.055
P/F Ratio		265.05 (70.70–592.85)	115.46 (31.25–295.71)	**<0.001***
CRP (mg/dL)		9.67 (0.05–27.23)	22.62 (1.10–200.00)	**0.011***
LDH (U/L)		717.35 (270.00–1570.00)	1047.00 (524.00–2239.00)	**<0.001***

adult patients with fever or under surveillance airway infections, plus one of: respiratory frequency >30 x / min, severe respiratory distress, or oxygen saturation (SpO2) <90% in room air. Because there are a lot of similarites between treatment of patients with mild symptoms and moderate symptoms, the classification of severity is divided into "mild-moderate" and "severe". Statistic analysis performed to determine CRP, LDH and its relationship to disease severity and mortality using SPSS 26.0 version.

RESULTS

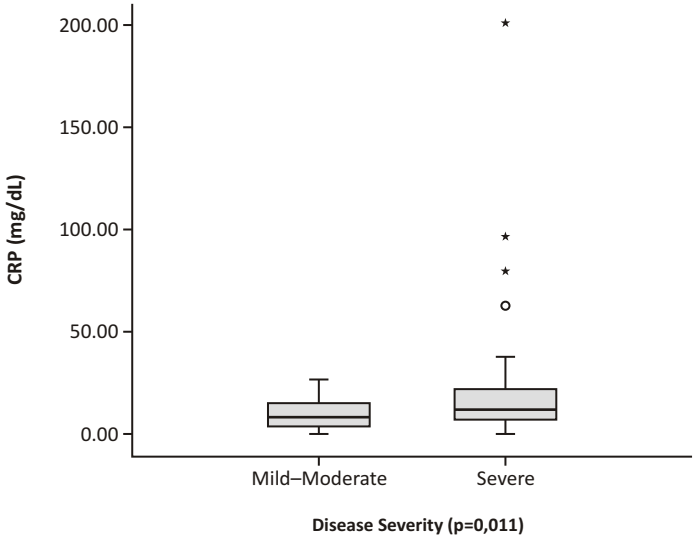
Data obtained from 69 patients with demographic characteristics are shown in table 1. Subjects include of 26 patients (37.7%) in the mild-moderate group and 37 patients in severe group (62.3%). Patient in severe group has a higher level of CRP (mean 22.62 mg/dL (1.10 mg/dL-200.00 mg/dL) compared than mild moderate group (mean 9.67 mg/dL (0.05 mg/dL-27.23 mg/dL). Patient in severe group also has a higher level of LDH (mean 1047.00 U/L (524.00 U/L-2239.00 U/L) compared than mild- moderate group (mean 717.35 U/L (270.00 U/L-1570.00 U/L). Statistical analysis showed that CRP and LDH associated with disease severity (p=0.011 and p<0.001) (Tabel 1; Graphic 1 and 2 ; ROC LDH with disease severity showed in Graphic 4). We also evaluate CRP and LDH with mortality. Patient in non survivor group has a higher level of CRP (mean 20.36 mg/dL (4.23 mg/dL-80.50 mg/dL) compared than survivor group (mean 17.86 mg/dL(0.05 mg/dL-200.00 mg/dL). Patient in non survivor group has a higher level of LDH (mean 1180.21 U/L (691.00 U/L-2239.00 U/L) compared than survivor group (mean 820.74 U/L (270.00 U/L-1570.00 U/L). Statistical analysis showed that CRPand LDH asscociated with disease mortality in hospitalized COVID-19 patients (p=0.034 and p=0.002) (Table 2). We evaluate CRP and LDH with degrees of hypoxemia by assessed P/F ratio.Statistical analysis showed that CRP did not correlate with degrees of hypoxemia (p=0.079) but LDH inverse correlate with degrees of hypoxemia (p<0.001, *Pearson* correlation = -0,489) (Graphic 3).

DISCUSSION

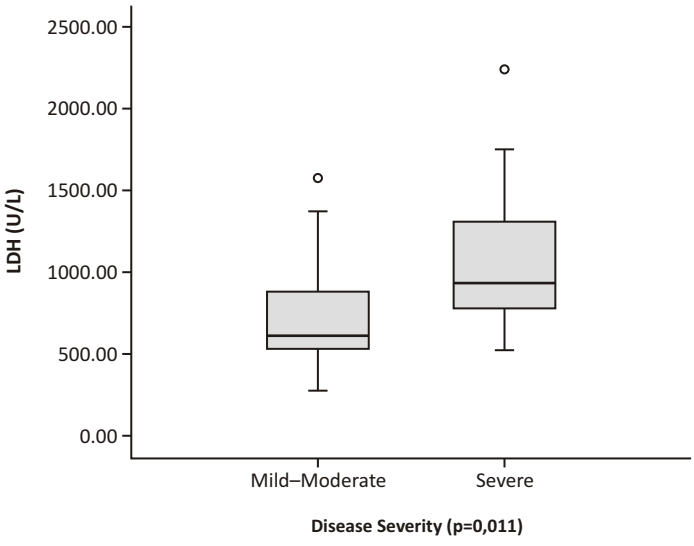
COVID 19 is known for its wide clinical feature and its rapid progressivity. SARS-CoV-2 has 4 days of incubation period (interquartile range, 2 to 7)[9] and has been purposed having three phases; early infection phase, pulmonary phase, and hyperinflammation phase. Early infection phase with symptoms fever, cough, myalgia,

TABLE 2
LDH and CRP on non-survival and survival group

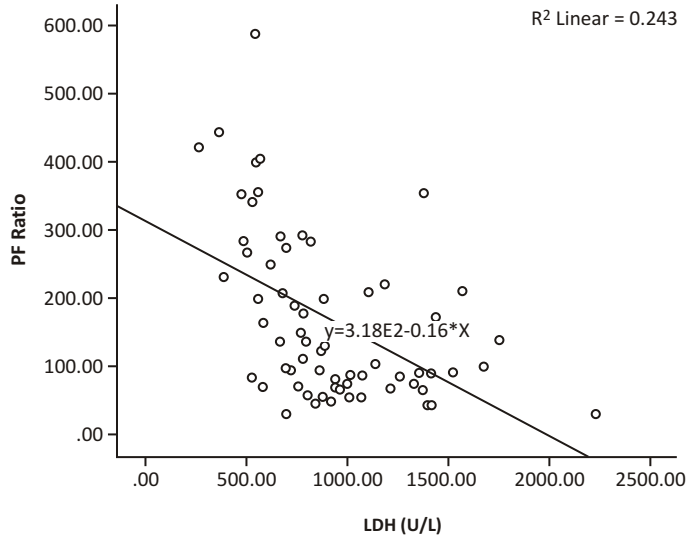
Variables	Mortality		*p-value*
	Survive (n=43)	Non survive (n=19)	
CRP (mg/dL)	17.86 (0.05–200.00)	20.36 (4.23–80.50)	0.034*
LDH (U/L)	820.74 (270.00–1570.00)	1180.21 (691.00–2239.00)	0.034*



Graphic 1. Association CRP with disease severity



Graphic 2. Association LDH with disease severity

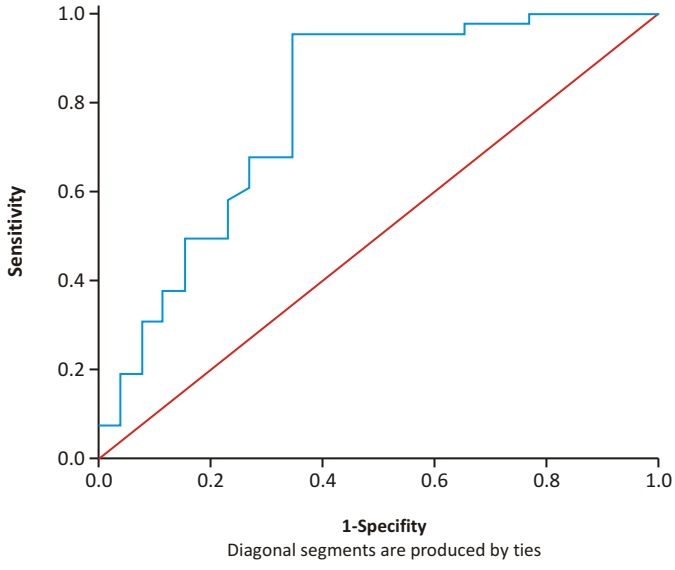


Graphic 3. Correlation LDH and disease severity by evaluation of PaO2/FiO2 (p<0.001, Pearson correlation = -0,489)

fatigue, sore throat, and headache; pulmonary phase with clinical manifestation tachypnea, shortness of breath, hypoxemia and respiratory failure; hyperinflammation phase with clinical features ARDS, shock, and multi-organ failure.[10] C-reactive protein (CRP) is an acute inflammatory protein produced primarily in liver hepatocytes but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. At inflammation sites, CRP can increase up to 1000-fold.[11] The average normal CRP plasma level is 0.8 mg/L, and can increase up to 500 mg/L within 24 – 72 hour after severe tissue damage.[12]

In COVID-19 patients, LDH and CRP might represent an expression of lung damage, and the respiratory distress consequent to the abnormal inflammation status.CRP is a hepatic protein regulated at the transcriptional level by the cytokine IL-6 and IL-1 and a reliable marker of acute inflammation. CRP correlates with the diameter of the lung lesion.[13] LDH is a general indicator of acute or chronic tissue damage and an inflammatory marker involved in energy production by conversion of lactate to pyruvate. LDH present in almost all body cells with the highest levels in the heart, liver, lungs, muscles, kidneys, and blood cells. LDH increased during acute and severe lung damage or interstitial lung infections.[13] In critically ill patients of COVID-19, the rise of LDH can indicate an increase in the activity and extent of lung injury.[14,13]

In another study, a small cohort of 27 patients, CRP correlated with CT findings and resulted significantly



Graphic 4. ROC Curve LDH to Disease Severity

increased at the early stage of severe COVID-19 before changes in the CT score.[13] In our study, the patient in the severe group has a significantly higher CRP mean value (22.62 mg/dL) (p=0.011). The patient in the severe group also has a significantly higher LDH mean value (1047 U/L) (p<0.001).Our study result is consistent with several studies. Hendry *et al.*, suggest that increasing LDH serum level has been associated with worse outcome. Patient with high LDH serum level (cut off 240–255 U/L) is 6 times more at risk of developing severe disease and 16 times more at risk of mortality. Tan *et al.* revealed the levels of C reactive protein (CRP) in the severe group at the initial and progression stages were higher than those in the mild group. CRP in severe COVID-19 patients increased significantly at the initial stage, before CT findings.[15] Gao *et al*. found that the level of CRP was significantly higher in the severe group (39.37 ± 27.68mg/L) than in the mild group (18.76 ± 22.20 mg/L) (p=0,011).[16] Wu, *et al*. revealed the LDH level in all patients was 495.1 ± 28.22 U/L (range 1581482 U/L). The LDH level in non-severe patients amounted to 442.0 ± 17.47 U/L, the higher LDH levels were found in the severe group with a LDH level of 1040.0 ± 158.3 U/L (n=87, p<0,01).[17] Our study revealed that LDH inverse correlate with P/F ratio (p<0.001, *Pearson* correlation = -0,489). This finding in line with Poggiali *et al*. that showed LDH had strong inverse correlation with the P/F ratio (p<0.0001).[13]

In conclusion, LDH and CRP can be a crucial indicator to predict severity and mortality for hospitalized COVID-19 patients and LDH may usefull test for predict early identification of patients who become respiratory failure or ARDS.

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