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Lactate dehydrogenase and C-reactive protein as predictors of severity and prognosis in corona virus disease 2019 (COVID-19) in Iraqi patients

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Abstract---The Objective of the Study:-To estimate whether the initial C-reactive protein (CRP) and Lactate dehydrogenase (LDH) levels are able to act as markers of severity and prognosis in COVID-19 adult patients. Patients and Method: This cross sectional study was conducted in the Marjan medical teaching city during the period from January 2021 to august2021. 100 Patients who complained from fever or chest symptoms were enrolled after laboratory confirmation of COVID19 via RT-PCR. Chest computed tomography scan(CT) was then performed to classify the patients into mild, moderate and severe, critical pneumonia groups according to world health organization(WHO)classification, initial plasma CRP level and LDH level were measured for all patients. Follow up and documentation were done for all patients. A thoracic radiologist interprets chest CT scan and produces a structured report. An informed written consent was obtained from each participant. Results: Cross sectional study of 100 cases with COVID 19 infection, mean age of patients (51.6 ± 15.5) years. 51%are females and 49% are male, (79%) of patients admitted to hospital and then get well and discharged, 16% died. CRP and LDH

increase in complicated patients with COVID 19 infection. Critical cases have high LDH than other types of severity. There is significant positive correlation between LDH and CRP. Conclusion: The level of plasma CRP and LDH was positively correlated to the development of complication and There is a significant difference between mean of LDH according to severity of disease in covid and There is a significant positive correlation between LDH and CRP so LDH and CRP early measurement in covid 19 may be useful as an earlier indicator for disease severity and risk of complication.

Keywords---corona virus, COVID-19, CRP, LDH, Marjan hospital, Babylon, Iraq.

Introduction

COVID 19 was discovered during the epidemic of pneumonia in Wuhan China in January 2020⁽¹⁾ Since then, the virus has spread all over the world, and as of 10 of march 2022, it has infected 450,229,635 people, including 6,019,085 deaths⁽²⁾ Patients with COVID 19infection may present with three main symptoms : fever, cough, and shortness of breath⁽³⁾as the pandemic progressed the symptoms was expanded to include :-headache, sore throat, the loss of taste (ageusia) , loss of smell (anosmia), myalgia , chills⁽⁴⁾ it has been reported that, in addition to common respiratory symptoms, patients with COVID-19 have gastrointestinal symptoms, mainly including diarrhea, nausea, and anorexia ^(5,6). Most of the hospitalized patients with COVID-19 have elevated CRP levels ⁽⁷⁾.Systemic inflammation, as measured by CRP, is strongly associated with VTE, AKI, critical illness, and mortality in COVID-19 ⁽⁸⁾. Accumulating evidence has indicated that in COVID-19 pneumonia CRP is markedly associated with the severity and prognosis of excessive inflammatory response. In this regard, CRP also acts as a direct participant in the pathological process as a biomarker of inflammation ⁽⁹⁾ Clinicians across the world are now using CRP as one of predictors of disease severity in COVID-19⁽¹⁰⁾.serum LDH was elevated in severe COVID-19 patients ⁽¹¹⁾ .The increased LDH level in patients with COVID-19, is associated with a higher risk of poor prognosis and higher mortality ^(12, 13). Serum LDH was validated for its usefulness as markers for evaluation of disease severity and monitoring the response to treatment in COVID-19 pneumonia ⁽¹⁴⁾.

Patient and Methods

Study Design

This cross sectional study was conducted in the Marjan medical teaching city during the period from January 2021 to august2021. 100 Patients who complained from fever or chest symptoms were enrolled after laboratory confirmation of SARS-CoV-2 viral nucleic acid via RT-PCR. Chest CT scan was then performed to classify the patients into mild, moderate and severe, critical pneumonia groups according to WHO classification, initial plasma CRP level and LDH level measured for all patients. Follow up and documentation was done for

all patients. A thoracic radiologist interprets chest CT scan and produces a structured report.

Sample Selection

1. Patient with fever, cough, dyspnea, other chest complaints.
2. PCR positive.
3. Age 18 years and older.
4. Completed lab work up.

Exclusion Criteria

1. Age younger than 18 years.
2. PCR negative.
3. Uncompleted lab work.

Sampling

A sample of 100 out of 150 patients was selected after eligibility to inclusion and exclusion criteria.

Data Collection

The data was collected by the researcher and assistant from the study participants directly and filled in a prepared questionnaire paper. The questionnaire paper was designed by the researcher.

The questionnaire paper included the followings

1. Demographic characteristics of study participants: name, age and gender.
2. Phone number.
3. Past medical history
4. Symptoms review
5. PCR result
6. CT result
7. CRP level
8. LDH level
9. Outpatient or admitted
10. Who classification of severity.
11. Any complication.
12. Outcome.

Clinical categories

The severity of the disease was classified according to the Guidelines for the Diagnosis and Treatment of New Coronavirus Pneumonia (fifth edition) (15). And categorized into 4 groups:

- Mild: patients with mild clinical symptoms and no pulmonary changes on CT imaging.

- Moderate: patients with symptoms of fever and signs of respiratory infection, and having pneumonia changes on CT imaging.
- Severe: patients presenting with any one item of the following:
 - a) Respiratory distress, respiratory rate $\geq 30/\text{min}$,
 - b) Oxygen saturation $\leq 93\%$ in resting condition.
 - c) Arterial partial pressure of oxygen (PaO₂) /oxygen concentration (FiO₂) $\leq 300 \text{ mmHg}$ (1 mmHg = 0.133 kPa).
- Critical: patients meeting any one of the following criteria:
 - a) Respiratory failure requiring mechanical ventilation.
 - b) Shock.
 - c) ICU admission requirement due to multiple organ failure.

Ethical considerations

1. The ethical approval was taken from hospital authorities.
2. A written informed consent was taken from all the study participants.
3. No conflict of interest.

Statistical Analysis

Statistical analysis for this study was done by SPSS 22. Frequency and percentages used for categorical data while continuous numerical data are represented as mean, median and standard deviation. Chi –square used for assessment of association between variables, person correlation show the correlation between continuous data. T test used for evaluation of the differences between mean and median of continuous variables. P-value of less or equal to 0.05 was considered statistically significant. The result presented as tables and/or graphs. Statistical analysis of the study was done by statistician who is Specialist in Community Medicine.

Results

Cross sectional study of 100 cases with COVID 19 infection, mean age of patients (51.6 $\pm$ 15.5) years. (51%) of patients are females and 49% of them are male, (79%) of patients admit to hospital and then get well and discharge, 64% of patients have complications and 44% of patients have multiple risk factors to get infection. As show in (Table 1).

Table (1): Distribution of variables

Variables		Frequency	Percentage
Gender	F	51	51.0
	M	49	49.0
outcome	Death	16	16.0
	Discharge	79	79.0
	Outpatient	5	5.0
Complications	Yes	64	64.0
	No	36	36.0
Risk factors	No	56	56.0

	Yes	44	44.0
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In (Fig 1), the severity of disease according to symptoms classified as (48%) of patients have moderate severity, 30% of them have critical symptoms and severity.

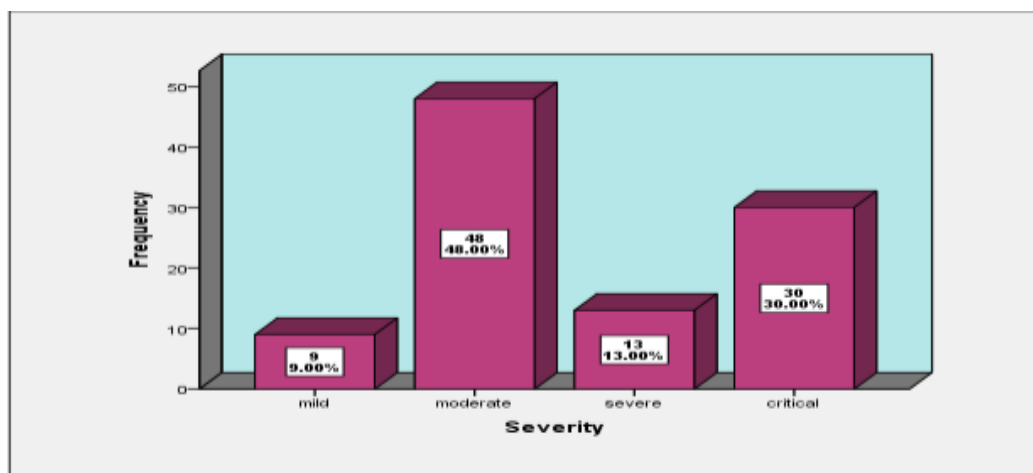


Fig (1): Distribution of patients according to severity

According to (Table 2), there is significant difference in mean of CRP according to presence of complications, CRP increase in complicated patients with COVID 19 infection. While there is no significant difference in mean of CRP according to presence of risk factors and gender.

Table 2: Difference between mean of CRP according to risk factors and complication of disease

Group		N	Median & Range	P-value
Gender	Female	51	20 (6 -184)	0.62
	Male	49	30 (8 -137)	
Risk factors	No	56	24 (6 – 184)	0.84
	Yes	44	25 (6 (170)	
Complications	No	36	18 (6 – 105)	0.018
	Yes	64	30 (6 – 184)	

P-value $\leq$ 0.05 (significant).

According to table 3, there is significant difference in mean of LDH according to presence of complications, LDH increase in complicated patients with COVID 19 infection. While there is no significant difference in mean of LDH according to presence of risk factors and gender.

Table (3): Difference between mean of LDH according to risk factors and complication of disease

Group		N	Mean $\pm$ SD	P-value
Gender	Female	51	551 $\pm$ 306.9	0.19
	Male	49	652 $\pm$ 445.1	
Risk factors	No	83	608.3 $\pm$ 404.6	0.82
	Yes	17	591.2 $\pm$ 356.4	
Complications	No	36	508.5 $\pm$ 176.1	0.026
	Yes	64	625.7 $\pm$ 452.7	

P-value $\leq$ 0.05 (significant).

There is significant difference between mean of LDH according to severity of disease, critical cases have high LDH than other types of severity. While there is no significant difference between mean of CRP according to severity of disease. As show in (Table 4).

Table (4): Difference between mean of LDH and CRP according to severity of disease

Severity		N	Mean	Std. Deviation	P-value
CRP	Mild	9	43.11	35.3	0.21
	Moderate	48	33.91	28.6	
	Severe	13	34.23	25.4	
	Critical	30	51.73	51.6	
LDH	Mild	9	571.11	132.4	0.012
	Moderate	48	502.37	266	
	Severe	13	553.53	287.5	
	Critical	30	787.73	540.2	

P-value $\leq$ 0.05 (significant).

According to table 5, there is significant positive correlation between LDH and CRP, but there is no correlation between age (LDH and CRP).

Table (5): Correlation between Age, LDH and CRP

		LDH	CRP
Age	Pearson Correlation	0.156	0.06
	Sig. (2-tailed)	0.122	0.55
LDH	Pearson Correlation	-	0.26
	Sig. (2-tailed)		0.009

According to table 6 the mean and SD of CRP according to severity of symptoms in patients with COVID as the following; mild (43.1 $\pm$ 35.3), moderate (33.9 $\pm$ 28.6), severe (34.2 $\pm$ 25.4) and critical (51.7 $\pm$ 51).

Table (6): Mean and SD of CRP according to types of severity

Variables	Mean $\pm$ SD
Mild	43.1 $\pm$ 35.3
Moderate	33.9 $\pm$ 28.6
Severe	34.2 $\pm$ 25.4
Critical	51.7 $\pm$ 51

According to table 7 the mean and SD of LDH according to severity of symptoms in patients with COVID as the following; mild (571.1 $\pm$ 132.4), moderate (502.37 $\pm$ 266), severe (553.5 $\pm$ 287.5) and critical (787.7 $\pm$ 540).

Table (7): Mean and SD of LDH according to types of severity

Variables	Mean $\pm$ SD
Mild	571.1 $\pm$ 132.4
Moderate	502.37 $\pm$ 266
Severe	553.5 $\pm$ 287.5
Critical	787.7 $\pm$ 540

Discussion

In patients with Covid-19, we identified notable differences in comorbidities and clinical presentations and lab features between patients who experienced severe illness and complication and those who did not. The aim of this work is to define the type of patients at risk of severe COVID-19 and to assess for certain predictors of severity. One hundred consecutive patients with diagnosis of CoVID-19 were included in this study and we found that the Mortality rate in this study was 16%, With the Recent evidence highlighted the relevance of various biochemical tests for the determination of severity, poor prognosis or mortality related to COVID-19 ⁽¹⁶⁾.Complication developed in 64% of patients in this study which reflect the importance of early identification of high-risk patient using clinical and laboratory features contribute to early prediction, diagnosis and efficient treatment of patients ⁽¹⁷⁾. In one of the early meta-analyses aimed at assessing the impact of comorbidities on the course and clinical outcome of COVID-19, it was found that about 31% of adult patients (2329/7608) had comorbidities, with hypertension being the most prevalent condition, followed by heart failure, diabetes mellitus and coronary heart disease ⁽¹⁸⁾ .These pre-existing comorbidities were found to be linked with the severity of COVID-19 ⁽¹⁹⁾ .In this study 56% of patient had comorbidities for covid 19 such as hypertension, diabetes, ischemic heart disease, chronic kidney and liver disease .COVID-19 patients with pre-existing comorbidities had a higher likelihood of death. These findings could potentially help doctors to sort out the most susceptible COVID-19 patients by comorbidities, take precautionary measures which could potentially reduce the number of fatalities in COVID-19⁽²⁰⁾.In the early stage of COVID-19 CRP levels were positively correlated with lung lesions and could reflect disease severity ⁽²¹⁾ and there is a positive correlation between the CRP levels of COVID-19 patients and their respective outcomes with regard to death ⁽²²⁾.High CRP levels in COVID-19 patients are strongly associated with the prognosis of COVID-19 which

must be employed within the clinical practice to guide COVID-19 disease severity (23). A recent study showed that about 7.7% of non-severe COVID-19 patients were progressed to severe disease courses after hospitalization (24). In this study when we investigated the effect of initial CRP level on severity and complication and prognosis of patients with laboratory-confirmed COVID-19 and we found that CRP levels are predictive factor of complication development, and independent of factors such as gender, severity and comorbidities, CRP increase in complicated patients with COVID 19 infection (p value 0.018) which is significant. This finding further supports previous studies findings; however, the Median and range of CRP in this study was 30 (6 - 184) while other study reported that patients with more severe symptoms had on average CRP concentration of 39.4 mg/L and patients with mild symptoms CRP concentration of (18.8 mg) (25). And In another study, the mean concentration of CRP was significantly higher in severe patients (46 mg/L) than non-severe patients (23 mg/L) (26). And the results of this study would suggest that the higher the initial CRP level in patients, the worse the patient outcomes but further investigation into the relationship between CRP and COVID-19 in the Iraqi population is warranted. In other studies elevated LDH values were associated with 6-fold increased odds of severe COVID-19 disease. More importantly, elevated LDH was associated with a >16-fold increase in odds of mortality. As such, patients' LDH should be closely monitored for any of signs of disease progression or decompensation (27). And LDH was associated with poor prognosis in patients with COVID-19 (28). In this study we also investigated the effect of LDH on the clinical course severity and complication and prognosis of patients with laboratory-confirmed COVID-19 and we found that LDH levels are predictive factor of complication development, and severity and independent of factors for gender, and comorbidities. LDH increase in complicated patients with COVID 19 infection. (P value 0.026) which is significant and supports these findings. However in this study Mean LDH was 625.7 ± 452.7 Which is higher than other studies for example in one study the LDH level in all patients was 495.1 ± 28.22 U/L (range 158-1482 U/L) (29), and in other study median LDH was 300 (227.5- 435.5) (30). There is also significant difference between mean of LDH according to severity of disease, critical cases have high LDH than other types of severity. (P value 0.012) and There is significant positive correlation between LDH and CRP (p value 0.009). Based on the analysis in this work, we can conclude that careful monitoring of clinical data, risk factors and disease biomarkers may enable early determination of COVID-19- severity, efficient patient management and possibly minimize the related mortality. Conducting CRP and LDH levels for all patients with COVID-19 to help anticipate disease course and guide care.

Limitation of the Study

1. Small sample size.
2. Short time period.
3. Single center study.
4. Inaccurate beliefs about COVID19.
5. Lack of knowledge.
6. People distrust of the medical system,
7. Inconvenience of seeking medical advice early.

Conclusions

The level of plasma CRP and LDH was positively correlated to the development of complication and There is a significant difference between mean of LDH according to severity of disease in covid and There is a significant positive correlation between LDH and CRP so LDH and CRP early measurement in covid 19 may be useful as an earlier indicator for disease severity and risk of complication.

Recommendations

1. Larger sample size.
2. Long period study.
3. Multicenter should be involved.
4. Community education about importance of seeking medical advice early.

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