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Estimation of Lactate Dehydrogenase Level In COVID-19 patients in tertiary care hospital Of Madhyapradesh And Its Implication In Foretelling Bad Outcome In Covid 19 Positive Patients

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Abstract

Introduction: Coronavirus disease 2019 has infected more than 8 million people within worldwide. There is a need to properly identify high-risk cases that are more likely to deteriorate even if they present mild diseases on admission.

Material & Methods: A case-control study was conducted GMC bhopal enrolling confirmed COVID-19 patients who were mild on admission. Baseline clinical characteristics were compared between patients with stable mild illness (stable mild group) and those who deteriorated from mild to severe illness (progression group).

Results: From Jan 18, 2021, to Feb 18, 2021, 85 confirmed COVID-19 patients were enrolled, including 16 in the progression group and 69 in the stable mild group. Compared to stable mild group (n = 69), patients in the progression group (n = 16) were more likely to be older, male, presented with dyspnea, with hypertension, and with higher levels of lactase dehydrogenase and c-reactive protein. In multivariate logistic regression analysis, advanced age (odds ratio [OR], 1.012; 95% confidence interval [CI], 1.020–1.166; P = 0.011) and the higher level of lactase dehydrogenase (OR, 1.012; 95% CI, 1.001–1.024; P = 0.038) were independently associated with exacerbation in mild COVID-19 patients.

Conclusion: Advanced age and high LDH level are independent risk factors for bad prognosis in mild COVID-19 patients. Among the mild patients, clinicians should pay more attention to those with high LDH levels.

Keywords: COVID-19, Severe pneumonia, Lactate dehydrogenase, SARS-CoV-2,ARDS,RTPCR

Introduction

Coronavirus diseases 2019 is a pandemic disease worldwide [1]. As of April 1, 2020, the total number of confirmed COVID-19 cases has surpassed 3.48 crore cases and 4.8 lakh deaths in india alone[2]. Research of clinical characteristics of COVID-19 patients began at January. [3]. Scientist reported that more than half of COVID-19 patients developed dyspnea at 8 days following the initial onset of illness, while the onset of acute respiratory distress syndrome had a median day of 9 days, just 1 day more than the onset of dyspnea, which will indicate a rapid diseases progression. Despite the fact that COVID- 19 patients have mild symptoms and signs in their early stage, about 9–32% of patients would eventually develop severe illness. The 28-day mortality rate of critically ill patients is over 65% [4]. we enrolled patients who were evaluated as mild COVID-19 on admission from a prospective cohort .

Some of the patients deteriorated to severe diseases. We then compared the baseline characteristics between the stable mild group and progression group, trying to assess the potential markers to predict whether the disease will progress or not.

Abbreviations

ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; HR: Hazard ratio; IQR: Interquartile range; LDH: Lactase dehydrogenase; OR: Odds ratio; SD: Standard deviation

Methods

Study design and participants

This was a case-control study for the treatment of COVID-19 patients. The study was approved by the Ethics Committee of GMC Bhopal and Hamidia Hospital. All patients who participated in the study gave informed consent.

From Jan 18, 2021, to Feb 18, 2021, we enrolled all 143 patients with confirmed COVID-19.[5]The severity or clinical condition of COVID-19 patients was classified into pneumonia, severe pneumonia, ARDS, sepsis, or septic shock [5]. In our analysis, we defined the patients with pneumonia as mild cases and patients with severe pneumonia, ARDS, sepsis, or septic shock as severe cases. Nineteen COVID-19 patients presented with severe cases on admission were excluded.The remaining 124 patients, pneumonia progressed to severe cases in 16 patients while ongoing mild diseases were reported in 69 patients . Thirty-nine patients were excluded from this study because of the short duration of follow-up. Finally, we enrolled 85 COVID-19 patients in this study. Patients with or without progression to severe cases were divided in the progression group or the stable mild group, respectively.All enrolled patients were followed up until study duration.

Data collection

The medical records of patients were analyzed by the research team of Gandhi medical college Bhopal. We obtained epidemiological, demographic, clinical, laboratory, and radiology data from patients' medical records. The data were reviewed by a trained team of physicians. The date of disease onset was defined as the day when the symptom was noticed. Symptoms, vital signs, laboratory values, chest CT scan, and treatment measures during the hospital stay were collected.

Statistical analysis

Categorical variables were described as frequency rates and percentages, and continuous variables were described using mean (standard deviation, SD) or median (interquartile range,IQR). Continuous variables were compared using t tests, and categorical variables were compared using the $\chi 2$ test or the Fisher exact test. The variates with P value less than 0.05 were included into multivariate logistic regression model to determine the potential independent factors. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 22.0 software (SPSS Inc). P value less than 0.05 was considered sta- tistically significant.

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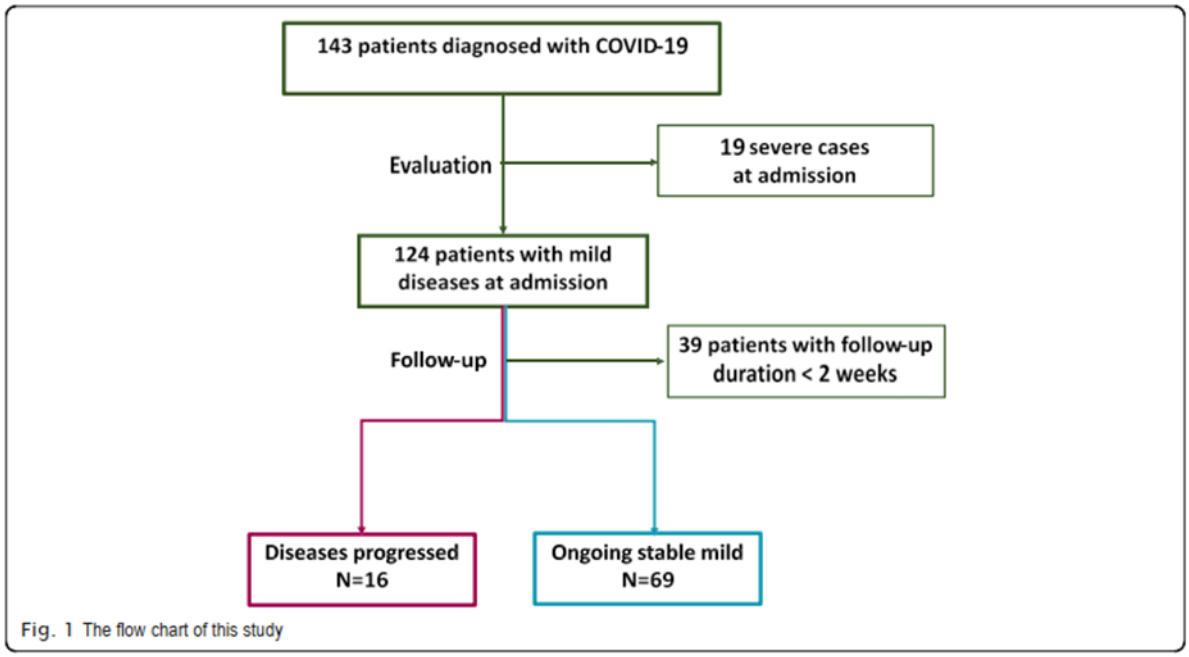

Fig. 1 The flow chart of this study

Table 1 Baseline characteristic of study population				
	All patients (n	Stable mild group (n	Progression group (n	P value
Age, years				<
Mean ± SD	46.6 ± 15.0	43.9 ± 14.0	58.2 ± 14.0	
Median, range	46 (15–81)	45 (15–80)	62 (30–81)	
Sex, Male	49 (57.6)	35 (50.7)	14 (87.5)	0.01
Symptoms				
Fever	71 (83.5)	57 (82.5)	14 (87.5)	0.635
Cough	47 (56.0)	38 (55.1)	9 (60.0)	0.728
Expectoration	29 (34.9)	22 (32.4)	7 (46.7)	0.293
Fatigue	39 (45.9)	33 (47.8)	6 (37.6)	0.455
Dyspnea	10 (11.8)	5 (7.2)	5 (31.3)	0.018
Diarrhea	10 (11.9)	9 (13.2)	1 (6.3)	0.679
Headache	5 (6.0)	4 (5.9)	1 (6.3)	1
Laboratory examination				
White blood count	4.8 ± 1.9	4.8 ± 1.8	5.1 ± 2.2	0.602
Neutrophils	3.2 ± 1.6	3.1 ± 1.6	3.5 ± 1.5	0.38
Lymphocytes	1.2 ± 0.7	1.2 ± 0.6	1.1 ± 1.2	0.418
Hemoglobin	135.7 ± 13.8	136.6 ± 13.6	132.3 ± 14.6	0.272
Platelets	184.6 ± 68.1	190.2 ± 73.0	160.5 ± 33.0	0.117
ALT	30.0 ± 68.1	29.0 ± 19.5	38.0 ± 14.1	0.517
AST	31.3 ± 18.8	29.7 ± 19.5	38.0 ± 14.1	0.114
Creatine	69.2 ± 22.7	64.8 ± 14.9	87.9 ± 37.8	0.029
Creatine kinase	150.4 ± 236.9	136.1 ± 241.7	212.2 ± 211.0	0.25
Troponin T	0.030 ± 0.309	0.024 ± 0.017	0.053 ± 0.054	0.052
Lactate	240.1 ± 84.3	222.4 ± 73.8	316.4 ± 86.4	<
NT-proBNP	85.7 ± 200.0	61.7 ± 79.3	189.6 ± 423.5	0.247

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C-reactive protein	23.6 ± 25.7	18.1 ± 20.2	47.0 ± 33.7	0.004
Radiology manifestation				0.528
Normal	4 (4.7)	4 (5.8)	0 (0%)	
Unilateral	8 (9.4)	7 (10.1)	1 (6.3)	
Bilateral involved	73 (85.9)	58 (84.1)	15 (93.5)	
Chronic medical illness				
Hypertension	26 (30.6)	17 (24.6)	9 (56.3)	0.032
Coronary heart	1 (1.2)	1 (1.4)	0 (0%)	1
Diabetes mellitus	11 (12.9)	9 (13.0)	2 (12.5)	1
Autoimmune	1 (1.2)	1 (1.4)	0 (0%)	1
Chronic liver	9 (9.4)	8 (11.6)	0 (0%)	0.174

Data are shown as n (%) or mean ± SD unless specified otherwise

Abbreviations: SD standard deviation, ALT alanine aminotransferase, AST aspartate aminotransferase, NT-proBNP N-terminal pro-B-type natriuretic peptide

Table 2 Multivariate logistic regression analysis of potential factors for disease progression

Covariate	Odds ratio	95% CI	*P*
Age	1.090	1.020–1.166	0.011
Female	0.113	0.014–1.571	0.113
Hypertension	0.212	0.521–	0.212
Dyspnea	2.319	0.268–	0.445
Creatine	1.032	0.977–1.090	0.264
Lactate	1.012	1.001–1.024	0.038
C-reactive protein	1.012	0.979–1.046	0.494

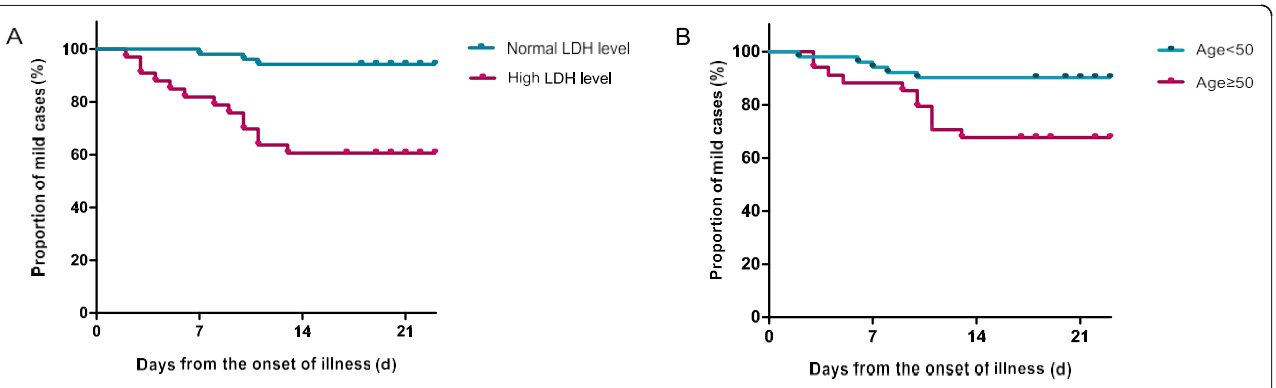

Fig. 2 Kaplan-Meier curves for diseases progression according to levels of LDH (a) and age (b). a Patients with LDH above the normal range were at significantly high risk of disease progress than those with normal levels of LDH (hazard ratio [HR], 8.31; 95% CI, 2.96−23.3, *P* < 0.001). b Patients aged 50 or older were at increased risk than patients whose age were younger than 50 (HR, 3.56; 95% CI, 1.35−10.2; *P* = 0.011). Abbreviation: LDH, lactase dehydrogenase

Results

As described in the method section, this case-control study enrolled 85 hospitalized patients with confirmed COVID-19, including 69 in the stable mild group and 16 in the progression group (Table 1). The mean age was 46.6 years (SD, 15.0), and 49 (57.6%) were male. The median duration from the first symptom to hospitaladmission was 5 days (IQR 4–7 days). Of 85 patients, 36 (42.4%) had 1 or more coexisting medical conditions. Hypertension (26 [30.6%]), diabetes (11 [12.9%]), and chronic liver diseases (9 [9.4%]) were the most common coexisting conditions. None reported chronic lung diseases, malignant tumor, and chronic renal diseases in this cohort. The most common symptom before admission was fever (71 [83.5%]), followed by dry cough (47 [56.0%]), fatigue (39 [45.9%]), and

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expectoration (29 [34.9%]). Dyspnea (10 [11.8%]) was less seen in the patients because all enrolled patients were mild at admission. Also, there were 10 (11.9%) patients initially presented with diarrhea. Two cases (2.4%) reported to be asymptomatic at admission. Radiology abnormalities were observed in 81 (95.9%) patients, 73 of whom showing bilateral pneumonia. CT scan or X-ray was charac- terized by multiple peripheral groundglass opacities.

In our cohort, pneumonia progressed in 16 patients. The median time from the onset of illness to severe pneumonia was 8.5 days (IQR, 4.25–10.75 days). When comparing the characteristics on admission between two groups (Table 1), we found that patients in the progression group were more likely to be older (58.2 ± 14.0 vs.43.9 ± 14.0, $p < 0.001$). Other potential risk factors included being males (87.5% vs. 50.7%, $p = 0.010$), presence of dyspnea (13.2% vs. 6.3%, $p = 0.018$), hypertension (56.3% vs. 24.6%, $p = 0.032$), the higher level of lactase dehydrogenase (LDH) (316.4 ± 86.4 vs. 222.4 ± 73.8, $p <0.001$), and C-reactive protein (47.0 vs. 18.1, $p = 0.004$).

Upon adjustment for potential confounding factors with the use of multivariate logistic regression analysis, two independent factors were associated with disease progression: advanced age (odds ratio [OR], 1.012; 95% confidence interval [CI], 1.020–1.166; P = 0.011) and the higher level of LDH (OR, 1.012; 95% CI, 1.001–1.024;P = 0.038) (Table 2).

Further, patients were stratified by the level of LDH and age. Compared with patients who had normal levels of LDH at admission, those with LDH above the normal range were at significantly high risk of disease progress (hazard ratio [HR], 8.31; 95% CI, 2.96–23.3, $P < 0.001$)

(Fig. 2a). Besides, patients aged 50 or older were at in- creased risk as well (HR, 3.56; 95% CI, 1.35–10.2; P = 0.011) (Fig. 2b). All patients in stable mild group and 68.7% (11/16) in the progression group were cured and discharged; the remaining 5 patients in the progression group were still hospitalizing in the ICU

Discussion

The study aim to focus on identifying high-risk COVID-19 patients for developing severe illness. To identify a small portion of high-risk patients among the whole population of mild patients, we excluded those who presented with severe illness on admission, thus only comparing patients with stable mild illness and those who deteriorated from mild to severe illness. The initial symptoms and signs in COVID-19 patients were usually very mild. However, as the disease progresses, some patients' symptoms would deteriorateAccording to CDC USA about 8–30% of patients would eventually develop severe illness and about 1–11% of patients would die [3]. Guan et al. [6] reported that 40% of ICU patients were non-severe on admission. With proactive screening of close contacts and quicker diagnostic procedures, this proportion may be even higher. Comparing the mild cases with or without deterioration will help clinicians identifying potentially critical patients earlier, allocating medical resources more reasonably, paying more attention to these patients, thus giving necessary interventions as early as possible. Previous studies have uncovered that there were numerous disparities in background illness, vital signs, and laboratory parameters between mild and severe patients, including lymphocytes, prothrombin time, creatine kinase, LDH, and so on [3, 6, 7]. However, which parameter dynamic change that initiates earlier remains unanswered.

LDH is a cytoplasmic glycolytic enzyme found in almost every tissue. Its elevation generally indicates tissue damage. Raised LDH was a common findings in patients infected with MERS-CoV [8–10], H7N9 [11, 12], and H5N1 [13]. It was reported to be an independent factor of mortality for patients with severe acute respiratory syndrome [14] and H1N1 infection [15]. It was also one of the biomarkers most strongly associated with ARDS mortality [16, 17]. Our finding of increased LDH in the early phase of severe COVID-19 cases suggested possible subclinical tissue damage. Although the virus binds to human angiotensin converting enzyme 2 (ACE2) receptor in the lung [18, 19], which explains why the lungs are the first organs affected, but as the disease progresses, various cytokine abnormalities and multiple organs dysfunction can be found in severe patients [3, 7], indicating systemic organ damage caused by the excessive activation of the immune system. LDH isoenzymes test can further help to locate damaged tissues or organs.

In this study, the comparison between the two groups showed differences in gender, history of

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hypertension, dyspnea symptom, creatinine, and C-reactive protein levels. These systemic factors also support that the pathophysiology of critically ill patients might be the systemic activation of immune response. History of hypertension was relatively rare as a factor in disease progression for an infectious disease; however, it was widely reported to be associated with disease severity of COVID-2019 [6, 7]. This was thought to be related to the virus binding receptor. Structural analysis suggested that SARS-CoV-2 might be able to bind to the ACE2 receptor [18, 19], which shared some homology with ACE and played a role in the renin- angiotensin system.

This study had several limitations. First, we did not measure viral load and some patients lacked coagulation function testing, which could be factors related to the severity of the disease. Second, we did not test the LDH isoenzymes due to limited resources. LDH isoenzyme analysis in the future may help to identify the source of increased LDH.

Conclusions

In this case-control study, advanced age and high LDH level were independent risk factors for deterioration in mild COVID-19 patients. Among the mild patients, clinicians should pay more attention to those with high LDH levels.

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