PROGNOSTIC VALUE OF LACTATE DEHYDROGENASE FOR IN-HOSPITAL MORTALITY IN CRITICALLY ILL PATIENTS WITH COVID-19

Biljana Eftimova
Clinical Hospital Stip, Republic of N. Macedonia beftimova@yahoo.com
Biljana Lazarova
Clinical Hospital Stip, Republic of N. Macedonia blazarova@yahoo.com
Strahil Gazepov
Clinical Hospital Stip,Republic of N.Macedonia gazepovstrahil@gmail.com
Zorica Naumovska
Faculty of pharmacy-Skopje, Republic of N. Macedonia zose@ff.ukim.edu.mk

Abstract: Purpose It is well known that COVID-19 patients may have increased serum lactate dehydrogenase (LDH) levels in the early stage, so LDH has been proved to be a prognostic factor for the severity and poor outcomes of coronavirus disease (COVID-19). The aim of the study was to evaluated the association of LDH and CRP with in-hospital mortality in critically ill patients with COVID-19 and their predictive value for prognosis.
Methodology A retrospective study was conducted in order to analyzed the clinical data of 55 critical COVID-19 patients. The patients were diagnosed with PCR test and critical cases met any one of the following criteria: respiratory failure and required mechanical ventilation, the occurrence of shock, and the combined failure of other organs that required intensive care unit monitoring and treatments, according to the diagnostic criteria of critical COVID-19. Clinical data including symptoms, detection of SARS-CoV-2, chest computed tomography (CT) images, CRP and LDH levels in serum were collected. According to chest CT images, we observed the fibrosis stages in all critical patients in this study. Most non-survivors died in the fibrosis stage. Statistical analysis of the data was performed and appropriate parametric and non-parametric test were conducted. Continuous variables were expressed as median (interquartile range) and compared with the Mann-Whitney U test. A pvalue of < 0.05 was considered statistically significant. Stat Graphics centurion 19 was used for statistical analysis.
Results Fifty five patients were enrolled into the study. The mean age was 67 ± 10 years; most of them were male (63.6%). Seventeen patients (31%) survived and 38 patient (69%) have died during the treatment in the ICU in the clinical hospital in Stip. The mean age in the survived group of patients was 66 ± 9 years; most of them were male (76.5%), whereas in the group of non-survivors mean age of patients was 68 ± 10 years with 42.1% women. Our results have suggested that the age does not influents the rate of survival (p=0.4). The obtained results confirmed that the LDH values depend on the gender. Our result have not reached statistical significance but there was evident tendency in higher values in LDH values in female patients on the admission in the ICU with p=0.068. Also the same tendency was confirmed for the influence of the LDH levels on survival of the Covid-19 patients in ICU with p=0.07. Limited number of enrolled patients may explain the tendency and higher number of patients included in the study is expected to confirm the statistical significance in influence of gender on LDH level, as well as influence of the LDH level on severe patient survival in ICU. In all patient population higher CRP values were confirmed (178±132) mg/L in the non-survivors group and (250±103) mg/L in the group of survivors. Our results have confirmed that there was statistically significant difference in the CRP values and rate of survival in ICU Covid-19 patients. There were statistically significant higher CRP values in the group on non-survivors in comparison to the group of survivors (p=0.03). Additionally, non-survivors had fewer days of hospitalization, shorter disease duration, shorter duration of fibrosis, and had dyspnea symptoms at disease onset ($P = 0.05$).
Conclusions LDH is a prognostic biomarker with acceptable accuracy for predicting in-hospital mortality in critically ill patients with COVID-19. This may help the physicians in the process of effective in identification of patients at high risk of death and rational prioritization of resources it order to initiate more aggressive treatments at an earlier phase to save patients' lives.
Recommendations LDH may play significant role as a biomarker for identification of COVID-19 patient population at high mortality risk and could help physicians in selection of patients eligible for more aggressive treatment initiation at early stage of ICU-admission.
Keywords: increased serum lactate dehydrogenase, covid 19, patients

1. INTRODUCTION

Over nineteen million people from August 7, 2020, has been confirmed infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) globally and the pandemic has caused over seven hundred thousand deaths worldwide so far according to Johns Hopkins University Coronavirus Resource Center (jhp.edu, last assessed

24.03.2021). Millions of cases have been reported worldwide, and the fatality rate was up to 7% (Li et al, 2020). However, the prognosis of critically ill patients is extremely poor. Identification of clinical and laboratory predictors of fatal forms progression is urgently needed for effective prioritizing resources for the patients at high risk of mortality.

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme which is widely expressed in tissues, which converts pyruvate, the final product of glycolysis, to lactate when oxygen is in short supply (Feron et al, 2009). LDH comprises two separately enclosed subunits, resulting in five isozymes, expressed in a specific organ: LDH 1 in cardiomyocytes, LDH 3 in lung tissue and LDH 5 in hepatocytes. Increased LDH was observed in different conditions such as hypoxia, tissue injury, necrosis, or malignancies (Kato et al, 2006). Tao et al. found that LDH was associated with death in patients with community acquired pneumonia (CAP) caused by viruses (Tao, et al 2018). Most of the patients in the early stage of COVID-19 have increased LDH levels, but whether serum LDH can be used as a marker related to COVID-19 treatment response is inconclusive. Computed tomography (CT) images of critically ill COVID-19 patients have characteristic manifestations in the fibrosis stages. Chest CT images are characterized by multiple ground-glass opacities (GGO). Critically ill cases often subsequently progressed to the fibrosis stage and showed consolidation, reticular pattern, and other fibrosis patterns on chest CT (Xie, et al 2020; Zhou, et al, 2020; Ye et al, 2020).

Coronavirus disease 2019 (COVID-19) is a disease that could cause multiple organ injuries including heart (Weiss et al, 2020; Wu, et al 2020), liver and kidney injuries (Zhang, et al, 2020; Cheng, et al, 2020). A growing number of studies demonstrated that elevated LDH value was associated with significantly increased mortality in patients with COVID-19 (Bousquet, et al, 2020). In most studies, were pooled and analyzed patients with different levels of COVID-19 severity, so this may prevent accurate evaluation of the relationship between LDH and disease progression and death because the majority of deaths happened in critically ill patients.

Therefore, our aim in this study was to evaluate the association of LDH with mortality in critically ill patients with COVID-19 in the intensive care unit (ICU) and its predictive value for clinical prognosis.

2. MATERIALS AND METHODS

Fifty five critically ill patients in the ICU of the Clinical hospital Stip, North Macedonia from December, 2020 to February, 2021 were enrolled in this study. The ICU for COVID-19 patients is new opened unit with 6 beds (December, 2020) and specialists anesthesiologists are responsible for the treatment of critically ill COVID-19 patients. The patients were diagnosed according to the World Health Organization interim guidance and critical cases met any one of the following criteria: respiratory failure and required mechanical ventilation, and the combined failure of other organs that required ICU monitoring and treatments, according to the diagnostic criteria of critically ill COVID-19 patients (WHO, interim guidance guidelines, 28.01.202). All 55 critically ill patients were transferred from infectious disease hospital department to ICU. All survivors were discharged following two negative PCR tests.

Demographic and clinical data including age, gender and the length of stay in hospital were collected. Peripheral venous blood sample was taken and routine blood examination including platelet counts, D-dimers, CRP and LDH was performed on day of admission. All the data were independently reviewed. Patients were divided into two groups according to the clinical outcomes of survival (discharge) or non-survival (death). Chest CT images were used to make a distinction between the pneumonia and fibrosis phases. All critically ill patients receive appropriate supportive therapies during the hospital stay and tromboprophylaxis with low molecular weight heparin (LMWH, 40-60mg enoxaparin/day) in line with adopted guidelines.

Statistical analysis of the data was performed and appropriate parametric and non-parametric test were conducted. Continuous variables were expressed as median (interquartile range) and compared with the Mann-Whitney U test. A p value of < 0.05 was considered statistically significant. Stat Graphics centurion 19 was used for statistical analysis.

3. RESULTS

Fifty five critically ill patients were enrolled into the study and 38 (69%) of them have died during the treatment in the ICU, while 17 patients (31%) of them survived. The causes of deaths included acute respiratory distress syndrome (ARDS), respiratory failure, shock and multiple organ dysfunction (MODS).

The baseline demographic and clinical characteristics are shown in Table 1. The mean age was 67 ± 10 years; most of them were male (63.6%). Compared with patients in the survival group, patients in the non-survival group were older (68 ± 10 years vs 66 ± 9 years). In the survival group most of the patients were male (76.5%), whereas in the group of non-survival group 42.1% were women. Our results have suggested that the age does not influents the rate of survival ($p=0.4$).

Table 1. Demographic characteristic of critically ill patients hospitalized in ICU unit

Parameters	All patients (n==55)	Survivors (n=17)	Non- survivors (n=38)	P-Value
Age (years)	67±10	66±9	68±10	0.4
Sex (male/female)	35/20	13/4	22/16	

In terms of laboratory findings, patients in the non-survival group had higher levels of CRP, but lower levels of platelets. Notably, in the non-survival group, LDH level was significantly higher than that in the survival group. As presented in Table 2 our results have suggested that the LDH values depend on the gender. Our result have not reached statistical significance but there was evident tendency in higher values in LDH values in female patients on the admission in the ICU (p=0.068).Also the same tendency was confirmed for the influence of the LDH levels on survival of the critically ill Covid-19 patients in ICU with p=0.07. We need more patients in our study for conformation of statistical significance of influence of gender on LDH level, as well as influence of the LDH level on patient survival in ICU.

Table 2. Influence of the gender on LDH (U/L) at admission in ICU

Gender	n	LDH (U/L)at admission in ICU		P-Value		n	LDH (U/L)at leave of ICU		P-Value
		mean	SD	0.068			mean	SD	0.07
male	35	578.686	382.391		survivor	16	497.25	259.832	
female	19	663.053	284.129		non-survivor	38	655.158	375.569	
Total	54	608.37	350.535		total	54	608.37	350.535	

Possible sources of elevated serum LDH levels during infection may be immunologic changes after SARS-COV-2 infection of the upper and lower respiratory tract which result in an early acute respiratory inflammatory response with consequent release of pro-inflammatory cytokines, including interleukin-1β, followed by inflammasome activation and production of active mature interleukin-1β which is a mediator of lung inflammation and fibrosis (Conti, et al, 2020). Lung parenchymal cells and/or local inflammatory cells may be potential sources of elevated LDH in serum (Drent, et al, 1996) and elevated serum values of LDH indirectly indicate lung tissue damage (Ding, et al, 2020). Lowest and highest values of LDH, together with more days with high LDH and a higher ratio of days with high LDH levels, are important for predicting the severity of critical COVID-19. As critical COVID-19 in the ICU is often combined with bacterial infection, LDH can convert pyruvate to lactate and might be the key enzyme for pneumococcal pyruvate metabolism and thus pneumococcal survival in blood (Gaspar, 2014).
In all patient population higher CRP values were confirmed (178±132) mg/L in the non-survivor group and (250±103) mg/L in the survivor group. Our results have confirmed that there was statistically significant difference in the CRP values and rate of survival in critically ill Covid-19 patients. As presented in Table 3 there were statistically significant higher CRP values in the group on non-survivor in comparison to the survivor group of (p=0.03) .

Table 3. Influence of CRP (U/L) at admission in ICU on survival of Covid-19 patients

	n	CRP (mg/l) value at admission in ICU		P-Value
		mean	SD	0.03
survivor	15	178	132	
non-survivor	27	250	103	
Total	42	224	118	

CRP have been confirmed as prognostic biomarker since the outbreak of COVID-19 and was also recommended as the early warning indicator for critically ill cases by Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). Han et al. have compared LDH with other prognostic biomarkers including CRP, lymphocyte and AST in predicting severe COVID-19 cases in patients with different levels of COVID-19

severity. They demonstrated that LDH had higher accuracy than CRP and lymphocyte in severity predicting. However, our study showed that LDH had a similar accuracy as CRP for predicting the in-hospital mortality in critically ill patients with COVID-19. Our finding may provide more accurate evaluation of the relationship between LDH and disease progression and in-hospital death.

The results of our study have confirmed that the days of hospital stay at ICU did not influence the rate of survival in the evaluated group of critically ill Covid-19 patients. (Table 4)

Table 4. Influence of the days spent in ICU on survival of Covid-19 patients

	n	**Days spent in ICU**		**P-Value**
		mean	SD	0.6
survivor	17	4.82	3.4	
non-survivor	38	5.1	5.16	
Total	55	5.	4.7	

4. DISCUSSIONS

The results of our analysis demonstrate an association between elevated LDH values and mortality in critically ill patients with COVID-19. LDH is an intracellular enzyme found in cells in almost all organ systems, which catalyzes the inter-conversion of pyruvate and lactate, with concomitant inter-conversion of NADH and NAD+ (Wu Y et al, 2017). The enzyme is composed by two major subunits (i.e. A and B), and is present in humans in five separate isozymes (LDH-1 in cardiomyocytes, LDH-2 in reticuloendothelial system, LDH-3 in pneumocytes, LDH-4 in kidneys and pancreas, and LDH-5 in liver and striated muscle). Although LDH has been traditionally used as a marker of cardiac damage since the 1960s, elevated LDH values can be result of multiple organ injury and decreased oxygenation with upregulation of the glycolytic pathway. The acidic extracellular pH due to increased lactate from infection and tissue injury triggers the activation of metalloproteases and enhances macrophage mediated angiogenesis. Severe infections may cause cytokine-mediated tissue damage and LDH release (Letko M et al, 2020). LDH is present in lung tissue (isozyme 3), infections in critically ill COVID-19 patients can be expected to release greater amounts of LDH in the circulation, as a severe form of interstitial pneumonia. However, the contribution of the different LDH isoenzymes to the LDH elevation observed in COVID-19 has not been determined. Additionally, LDH levels are elevated in thrombotic microangiopathy, which is associated with renal failure and myocardial injury (Lu et al, 2020; . Zhong K et al, 2020).

Many of the predictors and therapies currently being studied for COVID-19 are based on experience with the previous corona virus outbreak (Hamming I et al,2004). Because elevated LDH levels seem to reflect that the multiple organ injury and failure may play a important role in influencing the clinical outcomes in patients with COVID-19, we suggest that LDH level may be used as an important tool in determining prognosis in patients with COVID-19.

5. CONCLUSIONS

LDH is a favorable prognostic biomarker with high accuracy for predicting the in-hospital mortality in critically ill patients with COVID-19. This easily available biomarker will direct physicians worldwide to effectively prioritize resources for patients at high risk of mortality and to implement more aggressive treatments at an earlier phase to save patients' lives especially in the poor regions.

REFERENCES

Bousquet, G., Falgarone, G., Deutsch, D., Derolez, S., Lopez-Sublet, M., Goudot, F.X. et al. (2020). ADL-dependency, D-Dimers, LDH and absence of anticoagulation are independently associated with one-month mortality in older inpatients with Covid-19. Aging, 12(12), 11306-13

Cheng, Y., Luo, R., Wang, K., Zhang, M., Wang, Z., Dong, L. et al. (2020). Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney international. [Epub ahead of print]

Conti, P., Ronconi, G., Caraffa, A., Gallenga, C.E., Ross, R., Frydas, I., & Kritas, S.K. (2020). Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents, 34, 327-331.

Ding, C.Y., Peng, L., Lin, Y.X., Yu, L.H., Wang, D.L., & Kang, D.Z. (2019). Elevated Lactate Dehydrogenase Level Predicts Postoperative Pneumonia in Patients with Aneurysmal Subarachnoid Hemorrhage. World Neurosurg., 129, e821-e830.

Drent, M., Cobben, N.A., Henderson, R.F., Wouters, E.F., & van Dieijen-Visser, M. (1996). Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation. Eur Respir J,9,1736-1742.

Feron, O. (2009). Pyruvate into lactate and back: from the Warburg effect to symbiotic energy fuel exchange in cancer cells. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 92(3), 329-33

Gaspar, P., Al-Bayati F.A., Andrew, P.W., Neves, A.R., & Yesilkaya, H. (2014). Lactate dehydrogenase is the key enzyme for pneumococcal pyruvate metabolism and pneumococcal survival in blood. Infect Immun. 82, 5099-5109.

https://coronavirus.jhu.edu/, last assessed 24.03.2021

Hamming, I., Timens, W., Bulthuis, M.L., Lely, A.T., Navis, G., & van Goor, H. (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol., 203, 631–37.

Han, Y., Zhang, H., Mu, S., Wei, W., Jin, C., Tong, C. et al. (2020). Lactate dehydrogenase, an independent risk factor of severe COVID-19 patients: a retrospective and observational study. Aging, , 12(12), 11245-58

Kato, G.J., McGowan, V., Machado, R.F., Little, J.A., Taylor, J.T., Morris, C.R. et al. (2006). Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. Blood, 107(6), 2279-85.

Letko, M., Marzi, A., & Munster, V. (2020). Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol., 5, 562–69.

Li, L.Q., Huang, T., Wang, Y.Q., Wang, Z.P., Liang, Y., Huang, T.B., Zhang, H.Y., Sun, W., & Wang, Y. (2020). COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol., 92, 577-583.

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., et al. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet, 395, 565–74

Tao, R.J., Luo, X.L., Xu, W., Mao, B., Dai, R.X., Li, C.W. et al. (2018). Viral infection in community acquired pneumonia patients with fever: a prospective observational study. Journal of thoracic disease, 10(7), 4387-95

Weiss, P., & Murdoch, D.R. (2020). Clinical course and mortality risk of severe COVID-19. Lancet (London, England), 395(10229), 1014-5

World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/330893/WHO-nCoV-Clinical-2020.3-eng.pdf?sequence=1&isAllowed=y

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X, Xu, S. et al. (2020). Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA internal medicine. 2020 [Epub ahead of print]

Wu, Y., Cui, X., Wu, N., Song, R., Yang, W., Zhang, W., Fan, D., Chen, Z., & An, J. (2017). A unique case of human zika virus infection in association with severe liver injury and coagulation disorders. Sci Rep., 7, 11393

Xie, L.X. (2020). Interpretation of the 7th edition of the "diagnosis and treatment guidelines of coronavirus disease 2019 in China": Progress and challenges. Chronic Dis Transl Med. 23, 6(2), 75-78.

Ye, Z., Zhang, Y., Wang, Y., Huang, Z., & Song, B. (2020) Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol, 30, 4381-4389.

Zhang, C., Shi, L., & Wang, F.S. (2020). Liver injury in COVID-19: management and challenges. The lancet Gastroenterology & hepatology. 2020 [Epub ahead of print]

Zhou, M., Zhang, X., & Qu, J. (2020). Coronavirus disease 2019 (COVID-19): a clinical update. Front Med, 14, 126-135.

Zhong, K., Yi, Y., & Wei, W. (2020). Clinical characteristics and prognosis of community acquired pneumonia in autoimmune disease induced immunocompromised host: A retrospective observational study. World J Emerg Med., 11, 136–140.