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High level of lactate dehydrogenase and ischaemia–reperfusion injury regulate the multiple organ dysfunction in patients with COVID-19

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ABSTRACT

Background Multiple organ damage has been observed in patients with COVID-19, but the exact pathway is not known. Vital organs of the human body may get affected after replication of SARS-CoV-2, including the lungs, heart, kidneys, liver and brain. It triggers severe inflammation and impairs the function of two or more organ systems. Ischaemia–reperfusion (IR) injury is a phenomenon that can have disastrous effects on the human body.

Methods In this study, we analysed the laboratory data of 7052 hospitalised patients with COVID-19 including lactate dehydrogenase (LDH). A total of 66.4% patients were men and 33.6% were women, which indicated gender difference as a prominent factor to be considered.

Results Our data showed high levels of inflammation and elevated markers of tissue injury from multiple organs C reactive protein, white blood cell count, alanine transaminase, aspartate aminotransferase and LDH. The number of red blood cells, haemoglobin concentration and haematocrit were lower than normal which indicated a reduction in oxygen supply and anaemia.

Conclusion On the basis of these results, we proposed a model linking IR injury to multiple organ damage by SARS-CoV-2. COVID-19 may cause a reduction in oxygen towards an organ, which leads to IR injury.

INTRODUCTION

The COVID-19 pandemic caused by SARS-CoV-2 has been one of the deadliest diseases in human history. It has placed a huge burden on the healthcare system and the world encountered heavy economic losses. Various health complications have occurred after infection by the virus and the death rate is alarmingly high. Initially, it has been observed that the virus only causes respiratory distress. However, when the virus is transmitted across large populations, a diverse range of symptoms are reported, resulting from the targeting of different organs. Multiple organ failure has been observed in COVID-19, and damaged organs include the heart, lungs, kidneys and liver.[1] Furthermore, the nervous system and the haematological system have also been affected.[2]

The surface of the virus is mostly covered with spike (S) glycoproteins, which aid in viral entry by binding with a receptor known as ACE 2 (ACE2). The concentration of ACE2 is high in the lungs, heart and kidneys.[3] When the virus infects an organism, the immune system is stimulated and modulates the release of proinflammatory cytokines including interleukin (IL)-1β, IL-6, tumour necrosis factor-α, and type I and II interferons. The cytokine-induced signal transduction is mediated through the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway. STAT3 is a transcription factor in the JAK–STAT pathway which is activated by IL-6 through phosphorylation and results in elevated levels of tyrosine-phosphorylated STAT3.[4] Additionally, the levels of IL-6 also increase through a positive feedback mechanism by STAT3. The transcription factor binds to the IL-6 promoter to enhance the expression of IL-6.[5] Excessive accumulation of cytokines, that is, IL-6, and chemokines leads to a cytokine storm. This places a great strain on the body and high levels of inflammation can lead to organ damage.[6]

Furthermore, COVID-19 infection has also been shown to cause endothelial dysfunction, which may result in the constriction of blood vessels. Vasoconstriction is responsible for maintaining a homeostatic state of blood vessels by preventing unnecessary blood clots and ensures proper function of vascular smooth muscle cells.[7] ACE2 receptors are present on vascular endothelium, and after viral replication, the activity of ACE2 is reduced because SARS-CoV-2 occupies these receptors. ACE2 is a key modulator in the renin–angiotensin system (RAS), which is crucial to maintain blood pressure as well as electrolytic balance within the body. ACE produces angiotensin II (Ang II) and increases blood pressure by causing vasoconstriction. ACE2 counteracts this activity for balance. As RAS is unable to function properly during COVID-19 infection, endothelial dysfunction takes place.[8] Additionally, the endothelium plays a major role in reversing the damage of health complications like stroke, cancer, and kidney failure. Therefore, endothelial dysfunction can contribute to multisystem damage.[9]

Ischaemia is a serious health condition that can occur after endothelial dysfunction. As the blood flows towards an organ is restricted, it becomes deprived of oxygen. In the state of hypoxia, the electron transport chain in mitochondria is disrupted. Anaerobic glycolysis takes place in which lactate dehydrogenase (LDH) converts pyruvate into lactate by a reversible reaction. This results in low ATP production and lactate lowers the pH of the affected tissue, resulting in metabolic acidosis. This can disrupt the function of sodium–potassium pumps (Na^+/K^+–ATPase) and calcium pumps

Table 1 Concentrations of the blood biomarkers in patients with COVID-19

Biomarkers	Normal range	Sample values (N, mean±SD)	Status
RBC (million counts per µL)	4.7–6.1 (M), 4.2–5.4 (F)	3.8±0.9	Low
HB (g/L)	135–175 (M), 12.0–15.5 (F)	108±24	Low
HCT (%)	40–54.0 (M), 36.0–48.0 (F)	31.8±7.0	Low
CRP (mg/L)	10.0	141.7±103.3	Very high
WBC (µL)	4500–11 000	15 364.8±15 240.2	High
AST (U/L)	5.0–40.0	70.0±70.6	High
ALT (U/L)	7.0–56.0	77.0±88.6	High
LDH (U/L)	140–280.0	477.3±203.5	High

The levels of the first three biomarkers are different in men and women, denoted by M and F, respectively.
ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C reactive protein; F, female; HB, haemoglobin; HCT, haematocrit; LDH, lactate dehydrogenase; M, male; RBC, red blood cell; WBC, white blood cell.

(Ca^{2+}–ATPase). Therefore, sodium ions stay within the cells, whereas potassium ions are taken out. The surface of the endoplasmic reticulum has calcium pumps (Ca^{2+}–ATPase), which prevent excessive accumulation of calcium in the cytoplasm of cells. After the failure of these pumps, an abnormal concentration of calcium accumulates in the cells. This leads to an influx of water into the concentrated cells down the osmotic gradient; hence, the tissue swells and increases the risk of necrosis.[10]

Vasodilation occurs when oxygen is reintroduced to the affected organ. Oxygen molecules react with xanthine oxidase, that produces reactive oxygen species (ROS), that is, superoxide anion and hydrogen peroxide. High concentrations of ROS cause oxidative stress, which eventually leads to inflammation.[11] The strength of inflammation is alarmingly high, which can damage the swollen organ along with neighbouring organs. As a result, a very lethal condition of necrosis occurs.[12] Additionally, it has been observed that men have encountered more severe cases of COVID-19 than women. The cytokine storm can be curbed in women due to the presence of the oestrogen hormone. This hormone reduces the levels of IL-1β and IL-6 that are very active during the inflammatory response. Moreover, oxidative stress is also lowered by oestrogen, hence providing protection to women against COVID-19.[13] Our study aimed to investigate the pathophysiology of COVID-19 in critical cases which led to multiple organ failure and also taking gender difference into account.

METHODOLOGY

This study was approved by Shifa International Hospital Islamabad prior to collection of samples. We extracted data of 7052 patients with COVID-19 for blood analysis. The information included medical record number, date of admission, gender, age, and concentrations of various biomarkers. The biomarkers were red blood cells (RBCs), haemoglobin (HB), haematocrit (HCT), C reactive protein (CRP), white blood cell (WBC) count, aspartate aminotransferase (AST), alanine transaminase (ALT), and LDH. These biomarkers were highly useful to determine inflammation and tissue injury. We used the Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines for reporting this study.[14]

We shortlisted our samples on the basis of inflammatory marker CRP and high levels of WBCs; CRP values higher than 10 mg/L and WBC higher than 11 x 109/L of blood. In total, 709 patients were included in further analysis. SPSS software V.25.0 was used for statistical analysis and means with SD for each biomarker were used. The measured values of the biomarkers were compared with normal concentrations. Levels of RBC, HB and HCT were different in men and women, and gender difference was considered. The status of each biomarker with reference to its normal range in the human body was also stated. Pearson's correlation coefficient was used to determine the association between the two very important biomarkers, LDH and CRP. Moreover, the relationship between CRP and WBC was also determined. A p value less than 0.05 was considered statistically significant.

Data were divided on the basis of gender. Independent sample t-test was performed, which included group statistics. Group statistics consisted of biomarker levels, separate in men and women as indicated by mean values and respective SD. Equal variances were assumed for Levene's test for equality of variances,

Table 2 Gender-wise distribution of blood biomarkers in patients with COVID-19

Biomarkers	Male N (mean±SD)	Female (N, mean±SD)	95% CI		P value
			Lower	Upper	
RBC (million counts per µL)	98 (3.91±0.95)	46 (3.69±0.78)	−0.10	0.54	0.176
HB (g/L)	98 (111±2.52)	46 (100.1±1.79)	0.27	1.91	<0.009**
HCT (%)	98 (32.54±7.57)	46 (30.24±5.39)	−0.15	4.76	0.066
CRP (mg/L)	467 (152.59±101.62)	236 (120.21±103.42)	16.36	48.41	<0.001**
WBC (µL)	98 (15 389.18±16 779.11)	46 (15 312.83±11 454.40)	−5327.04	5479.75	0.978
AST (U/L)	56 (75.70±78.47)	18 (52.33±32.34)	−14.64	61.37	0.224
ALT (U/L)	59 (83.14±95.32)	20 (58.90±63.68)	−21.40	69.87	0.294
LDH (U/L)	125 (491.36±206.32)	63 (449.40±196.39)	−19.93	103.86	0.183

**P<0.01.
ALT, alanine transaminase; AST, aspartate aminotransferase; HB, haemoglobin; HCT, haematocrit ; LDH, lactate dehydrogenase; p, probability; RBC, red blood cell; WBC, white blood cell.

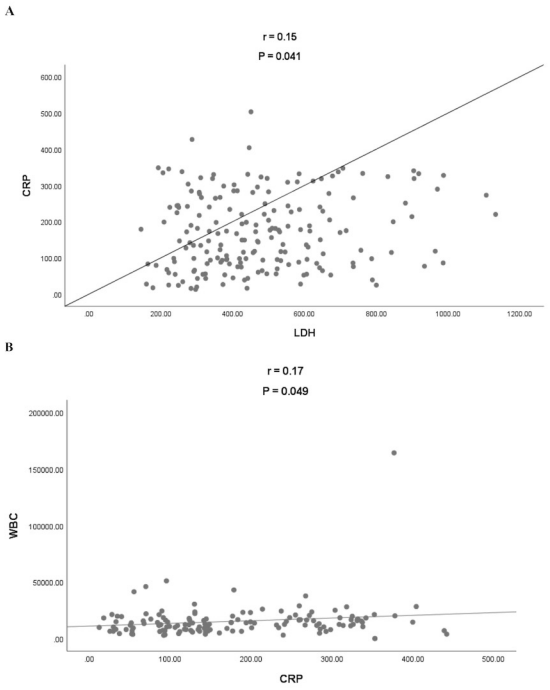

Figure 1 Scatter plot showing the correlation coefficient of biomarkers. The two graphs depict the correlations between (A) LDH and CRP and between (B) CRP and WBC. CRP, C reactive protein; LDH, lactate dehydrogenase; p, probability; r, Pearson's correlation coefficient; WBC, white blood cell.

95% confidence levels were also taken into account. Two-tailed significant values less than 0.05 and 0.01 were considered statistically different and highly statistically different, respectively.

RESULTS

The mean age of participants was 58±17 years. Levels of RBC, HB and HCT were lower in patients with COVID-19 than the normal values. In contrast, CRP concentration was particularly high in patients with COVID-19, and levels of LDH, WBC, AST and ALT were also higher than normal values (table 1).

After division of data based on gender, we observed that our sample included a higher percentage of men (66.4%) as compared with women (33.6%). Therefore, the proportion of men was approximately two times greater than that of women. Total levels of all biomarkers were higher in men than in women. There was a highly significant increase of HB ($t=2.64$, $p<0.01$) and CRP ($t=3.97$, $p<0.01$) in men than in women (table 2). Furthermore, there was a significant positive correlation between LDH and CRP (figure 1A). Notably, WBC and CRP shared the same correlation (figure 1B).

DISCUSSION

Our study is unique because we targeted multiple organ damage by COVID-19 in association with high level of LDH and ischaemia–reperfusion injury. Cavezzi *et al*[15] reported that SARS-CoV-2 can bind to RBCs, contributes to loss of oxygen and leads to hypoxia. This was consistent with our findings because we observed anaemia in our samples. As a result, RBCs and HB were unable to perform their functions properly. Therefore, our data mostly contained severe cases of COVID-19 as all study participants were hospitalised due to severe infection symptoms. Low haematocrit levels further confirmed the presence of anaemia.[16] Studies have reported that the aforementioned condition can lead to ischaemia-induced heart disease.[17]

The main finding in our study is the significant correlation between LDH and CRP. Both biomarkers showed a positive association with each other and their roles were highlighted in our model. Multiple organ damage was reported through elevated circulating LDH concentrations as it is present in almost all body organs. Therefore, its high levels showed injury to the heart, liver, lymph nodes, spleen, lungs, kidneys, pancreas, liver and striated muscles.[18] When an organ is injured, inflammation is initiated in the first step towards healing.[19] However, the presence of excessive cytokines can aggravate the situation through CRP. Stringer *et al*[20] observed that CRP is the most reliable biomarker associated with mortality in patients with COVID-19 due to excessive accumulation of cytokines and chemokines as an immune response. This is in line with our observations as elevated CRP levels were observed, therfore, showing the intensity of inflammation in our samples. Inflammation can happen anywhere in the body; elevated levels of CRP showed multisystem damage after its release during the process of reperfusion. This biomarker also showed a positive correlation with WBC that further supported the high level of inflammation in patients with COVID-19.

Omrani-Nava *et al*[21] reported that ALT and AST are linked with liver damage when their concentrations are higher than normal. Studies have also shown that elevated levels of AST indicate damage to the heart, skeletal muscle, kidney, liver and brain.[22] We observed a similar trend of AST in our data which eventually contributed to multiple organ injury. In our analysis, HB level was slightly higher in men than in women and was also significantly different between the two groups. When it comes to gender difference in association with COVID-19 severity, inflammation is the key factor to be considered. In our data, inflammation indicated by CRP level was significantly greater in men. It is reported that inflammation impairs the production of RBCs and haeme due to presence of excessive cytokines. Cai[23] has reported studies from China that support our findings; one study was done among severe cases that constituted 67% men and only 33% women. Another study consisted of 58% men where the data were taken from 552 hospitals and constituted 1099 patients. On the other hand, women were less prone to severe cases. Experiments conducted on mice revealed the importance of the protective role of oestrogen.[24]

We hypothesised that SARS-CoV-2 can cause multiple organ damage in severe cases by inducing IR injury. The inflammation which occurs in the process of reperfusion can lead to a cytokine storm because excessive cytokines and chemokines, including IL-6, are released at the site of infection as shown in our model (figure 2). Satarker *et al*[25] reported that levels of IL-6 were increased by STAT3 in the JAK–STAT pathway, which eventually increases the intensity of inflammation. We linked this pathway to our model through the cytokine storm. It is also reported that IL-6 sends signals to the liver to release CRP. CRP is then known to bind with Fc gamma receptor I (FcγRI) of IgG to initiate opsonisation that results in phagocytosis.[26] Macrophages take part in phagocytosis to curb the cytokine storm by removing inflammatory cells. Studies have shown that the presence of ROS hinders the function of macrophages, which leads to secondary necrosis and eventually chronic inflammation, hence resulting in inflamed tissue.[27]

We proposed a model to explain the mechanism of COVID-19 infection (figure 2). SARS-CoV-2 enters the bloodstream after binding to the ACE2 receptor expressed on an endothelial cell of a blood vessel. The virus causes endothelial dysfunction,

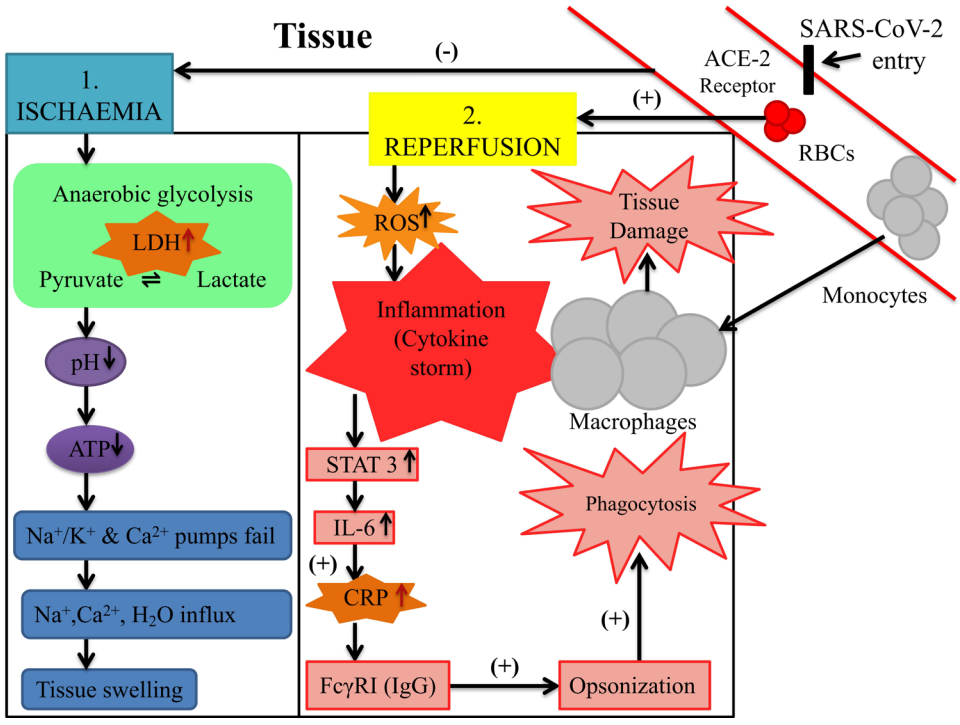

Figure 2 Proposed mechanism for COVID-19 infection in severe cases, leading to multiple organ failure. SARS-CoV-2 enters the bloodstream after binding with ACE2 receptor present on an endothelial cell of a blood vessel. The virus causes endothelial dysfunction, which results in vasoconstriction and induces ischaemia, the first step in IR injury, presented as number 1. Oxygen supply to an organ is restricted, which causes anaerobic respiration. This involves conversion of pyruvate into lactate by LDH. This results in low ATP levels and reduced pH levels, which cause Na^+/K^+–ATPase pumps and Ca^{2+}–ATPase pumps to fail. Consequently, sodium ions, calcium ions and water molecules are retained within the tissue, which leads to swelling. In response to ischaemia, reperfusion occurs, which is indicated as number 2, the second step of IR injury. In this process, excessive ROS are generated. A cytokine storm is initiated, which includes proinflammatory cytokines like IL-6. The JAK–STAT pathway is involved in the cytokine storm because STAT3 increases the levels of IL-6 and vice versa. IL-6 also signals the release of CRP to the site of inflammation. CRP binds with FcγRI on antibody IgG for opsonisation. Monocytes present in the bloodstream enter the injured tissue as macrophages to start the process of phagocytosis. However, due to oxidative stress, the macrophages are unable to perform their function properly. The great intensity of inflammation results in systemic changes. Ca^{2+}, calcium; CRP, C reactive protein; FcγRI, Fc gamma receptor I; IL, interleukin; IR, ischaemia–reperfusion; JAK–STAT, Janus kinase–signal transducer and activator of transcription; LDH, lactate dehydrogenase; Na^+/K^+, sodium/potassium; RBC, red blood cell; ROS, reactive oxygen species.

which results in vasoconstriction and induces ischaemia. Oxygen supply to an organ is restricted, which causes anaerobic respiration. This involves the conversion of pyruvate into lactate by LDH. This causes low production of ATP and reduced pH levels, which results in failure of Na^+/K^+–ATPase pumps and Ca^{2+}–ATPase pumps. Consequently, sodium ions, calcium ions and water molecules are retained within the tissue, which leads to swelling. In response to ischaemia, reperfusion occurs in which excessive ROS are generated. A cytokine storm is initiated, which involves the JAK–STAT pathway because more IL-6 molecules are activated through STAT3 and vice versa. This results in a positive feedback loop. CRP is then released to the site of inflammation through IL-6 signalling. CRP binds with FcγRI on antibody IgG for opsonisation. Monocytes present in the bloodstream enter the injured tissue as macrophages to start the process of phagocytosis. However, due to oxidative stress, the macrophages are unable to perform their function properly. The high intensity of inflammation results in organ damage and distant organs are affected too.

CONCLUSION

We conclude that cases of COVID-19 are more critical in men than in women. Moreover, our results strongly support our proposed model that COVID-19 induces IR injury in severe cases as suggested by the concentrations of biomarkers in our data. The presence of additional biomarkers, for example, ferritin, can further support our hypothesis as well as the consideration of comorbidities. Understanding the

Main messages

- Men are more affected by COVID-19 with relatively severe complications than women.
- We proposed that COVID-19 induces ischaemia–reperfusion injury in severe cases as suggested by the concentrations of biomarkers in our data.
- Understanding the pathophysiology of SARS-CoV-2 may help to develop efficient therapeutic treatments to overcome this pandemic completely and to prevent any future outbreaks too.

Current research questions

- To investigate the pathophysiology of COVID-19 in critical cases which led to multiple organ failure and also taking gender difference into account.
- What is the molecular phenomenon by which COVID-19 damages the cells of multiple body organs?

What is already known on the subject

► COVID-19 is a highly contagious disease which causes multiple organ damage in hospitalised patients, but the actual reason is not known.

pathophysiology of SARS-CoV-2 and its family of betacoronaviruses can help to develop efficient therapeutic treatments to overcome this pandemic completely and to prevent any future outbreaks too.

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