

Elevated Levels of Lactate Dehydrogenase Predicts Poor Outcomes For Patients with COVID-19: A Review

Abstract

In glucose (Glc) metabolism, lactate dehydrogenase (LDH) functions by changing pyruvate into lactate. Lactate dehydrogenase (LDH) release is induced via cell death, suggesting to disease caused by virus or pulmonary deterioration, such as inflammation of the lung triggered by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). A satisfactory evidence exists by binding elevated lactate dehydrogenase (LDH) levels to the development of coronavirus disease 2019 (COVID-19) complications.

Introduction

1. Coronavirus Disease 2019

In December 2019, pneumonia attributed to no known reason was recorded in a number of individuals in Wuhan, Hubei Province, of China (1)(2). These individuals were suffering from acute respiratory diseases (2). The infection hastily diffused from Wuhan to other places (3). The causative agent was defined as a novel coronavirus infection on January, 2020 (1). The novel causative microbe is called severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) by the World Health Organization (WHO) (1). This novel coronavirus (nCoV) is named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (4). The virus was called as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or 2019-nCoV because of its elevated consistency (~80%) to severe acute respiratory syndrome-coronavirus (SARS-CoV), that caused acute respiratory distress syndrome (ARDS) and elevated death-rate in the interim 2002–2003 (3).

Disease emerged from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was called coronavirus disease 2019 (COVID-19) and on March 11, the World Health Organization (WHO) announced a pandemic (5) (3). In spite of the attempts to control this virus dissemination, the epidemic propagated to many other cities in Asia and, by January 2020, infected individuals were defined in Europe countries (5). The World Health Organization (WHO) stated coronavirus disease 2019 (COVID-19) a universal health contingency of significant

international attention (4). The breakout of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was regarded to begin through a zoological origin spread correlated with shellfish emporium in Wuhan city (3). Then it was realized that individual to individual transport associated with the principal role in the consequent disease breakout (3).

1.1 SARS-CoV-2 Classification and Structure

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) belongs to the family Coronaviridae and order Nidovirales (1) (6). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a beta coronavirus (β -CoV) together with two notable pathogens, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) (6). Coronaviruses (CoVs) possess a positive-sense single-stranded ribonucleic acid (RNA) genome and a helical capsid with an envelope containing a lipid bilayer (5). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a single-stranded 29.9 kilo bases (kb) ribonucleic acid (RNA) virus (6) (7). Results presume vampires are the premier harbor of this viral agent (6). Vampires are improbable to be the animal that is a direct causative of the transmission of the virus to humans. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with genome sequence about 96.2% similar to a bat coronavirus RaTG13 – implicating bat as reservoir to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (8). Sequence analysis of the genome of coronavirus disease 2019 (COVID-19) showed that it has a potent homology to severe acute respiratory syndrome (SARS)-like coronaviruses (CoVs) that normally infect bats, and this is the reason why the pandemic is thought to be of zoonotic origin (5). Therefore, it is plausible to infer that novel coronavirus (2019-nCoV) could have transferred from vampires through an unidentified intermediary host to human beings (8). A research study proposed smuggled pangolins from Malaysia to China, as the possible virus origin, which could infect human being through potential alternative intermediate hosts such as turtles and snakes (9).

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded ribonucleic acid (RNA) viruses of about 30 kilo-bases (Kb) (3). Coronaviruses (CoVs) are widely categorized into four sorts; alpha (α), beta (β), gamma (γ), and delta (δ) depending on genomic structure (3). Alpha and beta coronaviruses (α and β CoVs) cause diseases to only mammals (3). Beta - coronaviruses

(β -CoVs) could lead to severe diseases and deaths in infected individuals, while alpha (α -CoVs) might cause asymptomatic or mildly symptomatic infectious diseases (7).

These coronaviruses (CoVs) have four constitutional proteins; spike (S), membrane (M), envelope (E) and nucleocapsid (N) (3). Spike (S) protein is considered a primary determinant of coronavirus (CoV) entry into the cells of the host (7). Spike (S) protein consists of a glycoprotein embossing from virus surface, specifying the coronaviruses (CoVs) divergence and their host (3). Spike (S) protein is composed of two functional subunits; S1 subunit is accountable for binding to the host cell receptor and S2 subunit is responsible for the incorporation of the membranes of both the coronavirus (CoV) and host cell. Spike (S) protein also attaches to angiotensin converting enzyme 2 (ACE2). Angiotensin converting enzyme 2 (ACE2) expression is elevated in lung, heart, ileum, kidney, and bladder. Angiotensin converting enzyme 2 (ACE2) was recognizably expressed on lung epithelial cells (3). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infects angiotensin converting enzyme 2 (ACE2) receptors on the surface of human cells (7). The human-to-human transmission happens by catching between the receptor-binding domain of coronavirus (CoV) spikes and the cellular receptor noticed as angiotensin converting enzyme 2 (ACE2) receptor (8). Soon after binding to their receptive receptor, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) enters host cells where they will face innate immunity (6).

1.2 Modes of Transference

Role of the Seafood Market in disseminating coronavirus disease 2019 (COVID-19) may not be clear (6). First coronavirus disease 2019 (COVID-19) infected individuals were associated with this market supposing that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was transmitted from animals to human beings (6). But, a genomic study declared proof that this beta coronavirus came from not known place, to the emporium where it disseminated hastily, though transfer from one individual to another may have happened previously (10). Cohort of diseased household individuals and medicinal employees assured the transmitting finding from one human to another human (6). In other words, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can be transmitted from person to another, and all individuals are susceptible to this infectious disease (11). Disease transfer from one human to another deems to be

incident through nearby contacts primarily through respiratory droplets of coughs or sneezes from infected persons (6) (8). Fomites may be a wide source of transmission (6). Authors have found mild virus protein levels in droplets and the microbeability of expanding exponentially explaining its elevated transferability (12). Droplet transmission elevates with nearer contact, within 1 meter range with coronavirus disease 2019 (COVID-19) infected individuals, elevating tendency of microbial entrance through mucous membranes of mouth, nose and eyes following exposing to probable infectious respiratory drops (8). Although in some literature airborne transferring was not mentioned, spread by sneezing or coughing, drops carrying coronavirus (CoV) have been airborne, and it is established coronavirus (CoV) remains animated in that location until 3 hours (13). Coronavirus disease 2019 (COVID-19) disseminates through both direct and indirect transmission, directly by contacting the infected individual or indirectly by touching the contaminated surfaces in the immediate surroundings (8). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has also been isolated from fecal swabs of infected individuals, referring to the probability of transmission via multiple ways (8). There are proofs that coronavirus disease 2019 (COVID-19) may disseminate through fomites (8). Researches showed that coronavirus (CoV) can remain alive for hours out the host, such as aluminium, sterile sponges or latex surgical gloves, drifting likelihood of transfer through contact (14). A notable article showed specimens obtained from WC utensils, were positive, indicating it a probable source of transmitting, although the negative results of specimens were following purgation (15).

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) incubation period is in the interim from 3 to 7 days and coronavirus disease 2019 (COVID-19) is infectious in latent interim (8). A notable research article showed mean incubation interim was 5.2 days (16). Incubation period can be from 19 to 24 days although case definitions usually regard a 14 day overtone (6).

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is immensely transmissible in human beings, particularly in the geriatrics and individuals with underlying comorbidities (8). Fenizia *et al.* (2020) showed findings provided that in utero vertical transmission was possible in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-positive pregnant females, agreed with previous researches (17).

1.3 Risk Factors

Coronavirus disease 2019 (COVID-19) is observed frequently in adult men with ages ranged from 34 to 59 years (18). The most occurrence of severe cases is in adults with ages more than 60 years, and in patients with underlying sufferings, as cardiovascular (CV) and diabetes mellitus (DM)(19)(6). It has been documented that individuals with diabetes mellitus (DM), hypertension (HTN), and coronary artery diseases (CAD) are more possible to have a poor prognosis, than that in individuals without these diseases (20). Severe complications can be also correlated with co-infections of bacteria and fungi (6). It is found that children are less probably to experience the disease and if happens exhibit more moderate symptoms than adult cases (6).

1.4 Symptoms and Complications of COVID-19 Infection

The predominant symptoms of coronavirus disease 2019 (COVID19) at the initiation of the disease are fever, dry cough, fatigue, or myalgia (1). A study showed that fever (found in ~99% of infected cases), cough (~50% of infected cases), and respiratory difficulty (~33% of infected cases) are the most common complaints of coronavirus disease 2019 (COVID-19) infection (5). Moreover, the commonest symptoms of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection involve dyspnoea, chest pain, and fatigue (6). Nearly one half of the infected individuals experience dyspnea after 1 week (2). Prevalent disease presentations involve headache, dizziness, abdominal pain, diarrhoea, nausea, and vomiting (6). It was found that about 75% infected individuals complained from bilateral pneumonia (6). In addition, about 80% of infected individuals have mild-to-moderate symptoms (5). The remainder have severe enough disease to entail hospitalization (5). Upper respiratory tract (URT) symptoms such as nasal congestion and runny nose are scarce (2). The dominant clinical characteristics exhibited by infected persons during the coronavirus disease 2019 (COVID19) pandemic are respiratory features (5).

Some infected individuals have moderate disease presentations with no have or not developing pneumonia and originally heal after 1 week (2). Besides that the coronavirus disease 2019 (COVID19) cases undergo moderate disease manifestations in their early phase, nearly 8 to 30% of infected individuals might ultimately progress acute disease (21). It was mentioned that the 28-day death rate of stringent patients was more than 60% (21). Literature have presumed that coronavirus disease 2019 (COVID-19) causes the development of severe pneumonia, other complications, and even mortality, particularly in high-risk cases (1). The most common complication was acute respiratory distress syndrome (ARDS), followed by acute cardiac injury

(ACI) and shock (1). The commonest neurologic symptom was olfactory and/or taste anomalies and the most predominant gastrointestinal (GI) symptom was anorexia (1). Infected individuals with severe coronavirus disease 2019 (COVID-19) infections are possibly to have some neurologic and gastrointestinal (GI) symptoms. Suffering from acute organ injury was more commonly recognized in severe coronavirus disease 2019 (COVID-19) patients (1).

Infected individuals may abruptly worsen and progress to acute respiratory distress syndrome (ARDS) (2). It is broadly noticed that aerobic presentations of coronavirus disease 2019 (COVID-19) are mostly heterogeneous, ranging from minimal symptoms to considerable hypoxia with acute respiratory distress syndrome (ARDS) (3). Severe cases showed that patients develop acutely acute respiratory distress syndrome (ARDS), sepsis, and coagulopathy (2). In the report from Wuhan, the period between the emergence of symptoms and the progress to acute respiratory distress syndrome (ARDS) was about 9 days, presuming that the respiratory symptoms might develop acutely (18). A study documented that some infected individuals developed acutely to acute respiratory distress syndrome (ARDS) and septic shock, which was ultimately succeeded by multiple organ failure and 10% of infected individuals deceased (6). Acute respiratory distress syndrome (ARDS) development and extensive lung deterioration in coronavirus disease 2019 (COVID-19) are further regarding that angiotensin converting enzyme 2 (ACE2) could be a way of entry for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as angiotensin converting enzyme 2 (ACE2) is amply identified on ciliated airway epithelial cells and alveolar type II cells in human beings (6). Severe manifestations such as hypoxaemia, acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute cardiac injury (ACI), liver injury, and acute kidney injury (AKI) have been recorded among coronavirus disease 2019 (COVID-19) cases (22-23). A study among 99 patients revealed that about 17% infected individuals progressed to acute respiratory distress syndrome (ARDS) in whom 11% deceased as a result of multiple organ failure (22). A study showed that the median period from first symptoms to development of acute respiratory distress syndrome (ARDS) was 8 days (6). Severely coronavirus disease 2019 (COVID-19) infected individuals might break down acutely to experience multiple organ damage, impaired immune response, and even mortality (11). Epidemiological investigations presented that mortalities are elevated in elder people and the occurrence of death is less among infected children (3).

1.5 COVID-19 Biomarkers

Different biomarkers are actually under search for participation in prediction in coronavirus disease 2019 (COVID-19) patients (24). Patients with coronavirus disease 2019 (COVID-19) exhibit laboratory anomalies including lymphopenia, prolonged prothrombin time (PT), and higher lactate dehydrogenase levels (6). Higher alanine aminotransferase (ALT), lactate dehydrogenase (LDH), high-sensitivity cardiac troponin I (hs-cTnI), and urea levels have been recorded to be associated with coronavirus disease 2019 (COVID-19) gravity (25-26). A study showed higher levels of both lactate dehydrogenase (LDH) and myoglobin (MB) in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infected individuals (1). Intensive care unit (ICU)-admitted patients experience more lab test anomalies in comparison with non-intensive care unit (non-ICU) cases (18). Some severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infected individuals had higher aspartate aminotransferase (AST), creatine kinase (CK), creatinine, and C-reactive protein (CRP) levels (27). In addition, coronavirus disease 2019 (COVID-19) cases have elevated levels of interleukin-1 (IL-1), interferon-gamma (IFN- γ), interferon gamma-induced protein 10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1) (18). Intensive care unit (ICU)-admitted cases observed to have elevated levels of granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1A (MCP-1A), macrophage inflammatory proteins A (MIP1A), and tumor necrosis factor-alpha (TNF- α). Lactate dehydrogenase (LDH) is an interesting biomarker, primarily as higher lactate dehydrogenase (LDH) levels have been bound to deteriorating outcomes in infected individuals with other viral diseases in the bygone (24). Findings in coronavirus disease 2019 (COVID-19) individuals supposed noticeable variations in lactate dehydrogenase (LDH) levels between diseased individuals and with no acute infection (28). An increasing number of studies indicated that higher lactate dehydrogenase (LDH) level was correlated with considerably elevated mortality rates in coronavirus disease 2019 (COVID-19) patients (23).

Coronavirus disease 2019 (COVID-19) presentations differ from moderate to acute respiratory distress syndrome (ARDS) tangling diagnosis, disease estimation, and disease surveillance (29). Therefore, of importance is assuring a patient's status in an appropriate method. Biomarkers are quantitative measures implemented medically for various situations indicating morbid progression. When estimating a coronavirus disease

2019(COVID-19) infected individual, biomarkers can be of benefit for clinicians in initiating management and monitoring the disease closely. A study proposed obvious proof of the way the levels of biomarkers might alter according to gravity of coronavirus disease 2019 (COVID-19). This is beneficial in medical practice to conduct management and admitting to intensive care unit (ICU). Therefore, lactate dehydrogenase (LDH) levels monitoring may improve prognosis and lessen the incidence of death (29). In other words, early recognition of severe coronavirus disease 2019 (COVID-19) is necessary for particular or specified treatment, involving antiviral therapy, organ support and intensive care unit (ICU) care, to ameliorate the prognosis (11). To date, neither a vaccine nor a particular therapy with a assured result has been available to coronavirus disease 2019 infected cases (1).

2. Lactate Dehydrogenase

2.1 Lactate Dehydrogenase Structure and Isozymes

Lactate dehydrogenase (LDH) is an intracellular enzyme present in nearly all organs' cells of the body (24). Lactate dehydrogenase (LDH) is a cytoplasmic enzyme broadly expressed in tissue cells involving the heart, liver, muscles, kidneys, lungs, and in bone marrow, and in addition, red blood cells (RBCs) having mild levels (5) (23) (30). This enzyme is with 134 kilo Dalton (kDa) molecular weight and consists of four peptide series of two kinds: M (or A) and H (or B), each controlled by distinct genetic material (31). Lactate dehydrogenase (LDH) is one of oxidoreductases, with an enzyme commission number EC 1.1.1.27 (30). Lactate dehydrogenase (LDH) identifies five isomeric kinds collected in tetramers of any of muscle (M) and heart (H) subunits (30). This enzyme is found in human beings in five distinct 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) (23-24). The isozymes known as LDH-1 to LDH-5, are everyone exhibiting peculiar expression in various body tissue cells (30). The peculiar expression of lactate dehydrogenase (LDH) is indicating its necessity as an analytical marker for diagnosis. Isozyme LDH-1 has four heart subunits (4H) and is found in the cardiac cells. Isozyme LDH-2 has three heart and one muscle subunit (3H1M) and is dominated in the reticuloendothelial system and red blood cells (RBCs). The LDH-3 isozyme is composed of two heart and two muscle subunits (2H2M) and is principally present in lungs. Isozyme LDH-4 consists of one heart and three muscle subunits (1H3M) and is particularly found

in kidneys. The LDH5 isozyme consists of four muscle subunits (4M) and is dominated in liver and skeletal muscle (30).

2.2 Lactate Dehydrogenase Mechanism of Action

Lactate dehydrogenase (LDH) transports hydrogen and catalyzes oxidation of L-lactate to pyruvate with nicotinamide adenine dinucleotide (NAD^+) as a hydrogen acceptor, with a two-faced response (31). The enzyme converts pyruvate, which is the final component of glycolysis, to lactate when oxygen is in short supply (23). Lactate dehydrogenase (LDH) is an intracellular enzyme included in anaerobic glycolysis that catalyzes the oxidation of pyruvate to lactate (11). Lactate dehydrogenase (LDH) elevates the rate of the simultaneous inter-conversion of pyruvate to lactate and the reduced form nicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD^+) by 14 orders of magnitude (32-33). The chemical reaction carries out by transferring a hydride ion from reduced form nicotinamide adenine dinucleotide (NADH) to pyruvate at its second carbon atom (33). The machinery comprises linking of reduced form nicotinamide adenine dinucleotide (NADH) to the enzymes as an initial stage. Abundant residues at the vigorous locus are included in this linking. As soon as reduced form nicotinamide adenine dinucleotide (NADH) is linked, it favors the lining of lactate, by the interaction between the reduced form nicotinamide adenine dinucleotide (NADH) ring and lactate dehydrogenase (LDH) molecules. Transport of a hydride rapidly happens in both ways leading to formation of two combinations, LDH- NAD^+ -lactate and LDH-NADH-pyruvate (33). Next, pyruvate splits from the enzyme initially, and nicotinamide adenine dinucleotide (NAD^+) liberates (34). Percent of detachment of reduced form nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide (NAD^+) is the rate-limiting point in this reaction, and the eventual transformation of pyruvate to lactate resulting in rejuvenating of nicotinamide adenine dinucleotide (NAD^+) is thermodynamically employed in the reactivity (34). Lactate dehydrogenase (LDH) is enzyme catalyzes the reversible oxidation of lactate to pyruvate and is necessary in anaerobic glycolysis, the process in which the body gains its energy from carbohydrate disrupt (35). When cells expose to anaerobic or hypoxic situations, the synthesis of adenine triphosphate (ATP) by oxidative phosphorylation breaks down (LDH-21). This process requires cells to produce energy by metabolic alternative (30). As a result, lactate dehydrogenase (LDH) is regulated in these situations to serve necessity of energy release.

Lactate resulted during anaerobic transformation of glucose (Glc) faces the metabolic end (30). No further metabolism occurs in any tissue except liver (36). Lactate is introduced to bloodstream and transferred to liver, where lactate dehydrogenase (LDH) accomplishes reversible response of transforming lactate to pyruvate via Cori cycle (36).

The effective position of the enzyme is in its substrate-binding pocket and holds inducible crucial His-193, Asp-168, Arg-171, Thr-246, and Arg-106 (30). Lactate dehydrogenase (LDH) isozymes are all constitutionally quite analogous; but, each is with specific vivid characteristics caused by variations in charged amino acids (AAs) surrounding the effective locus (37). Both lactate dehydrogenase (LDH) subunits, the M subunit and H subunit, keep the identical effective locus constitution and the amino acids (AAs) taking part in the response (30). In the tertiary constitution, alanine (Ala) of M-chain is substituted with glutamine (Gln) in H-chain. Alanine (Ala) is a nonpolar amino acid (AA), while glutamine (Gln) is a positively charged amino acid (AA), thus offering various biochemical characteristics to these two subunits. H subunit may link quicker but possess fivefold decreased effective action in comparison with M-subunit. Lactate dehydrogenase A (LDHA) subunit has a net charge of -6 and shows an elevated inclination towards pyruvate, thus transforming pyruvate to lactate and reduced form nicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD⁺) (30). Further, lactate dehydrogenase B (LDHB) has a net charge of $+1$ and exhibits an elevated inclination towards lactate, leading to favored transformation of lactate to pyruvate and nicotinamide adenine dinucleotide (NAD⁺) to reduced form adenine dinucleotide (NADH) (38).

The subunit constitution of the lactate dehydrogenase (LDH) enzyme (H and M subunits) differs among tissues (39-40). This difference is attributed to variation in the metabolic averages, energy demands, and task of tissues, which exhibits in their lactate dehydrogenase A:lactate dehydrogenase B (LDHA: LDHB) proportion. Roughly 40% of lactate in circulation is liberated from skeletal muscle. Consequently, lactate is taken up mainly by liver and kidney, where it suffers oxidation for synthesizing glucose (Glc) molecule. In brain, almost 10% of lactate oxidizes to power 8% of cerebral energy requirements during resting states, and lactate remnant is liberated in circulation. Hyperlactatemia and physical stress may result in absorption of lactate, hence, boosting 60% of brain metabolism, together with participation of cerebral lactate oxidation up to 33% (39-40).

Lactate dehydrogenase (LDH) mitochondrial existence is reported by many researches (30). L-lactate, the substrate for mLDH, is transferred to mitochondria through L-lactate/H symporter and L-lactate/pyruvate and L-lactate/oxaloacetate antiporters. Thereafter, mLDH favors oxidation of L-lactate to pyruvate in mitochondrial matrix. As cancer cells demand higher energy, glycolysis turns higher in cancerous cells, and mitochondrial L-lactate dehydrogenase (mLDH) plays a role in hastening the oxidative phosphorylation processes (30).

Lactate dehydrogenase (LDH) is immanent in keeping homeostasis when oxygen is absent (30). Oxygen concentrations in the muscle tissues decrease rapidly in intense practice. As oxygen is usually the ultimate electron acceptor of the electron transport chain (ETC), the chain turns off along with adenine triphosphate (ATP) synthase. In spite of that, muscle cells keep functioning by synthesizing adenine triphosphate (ATP) through nicotinamide adenine dinucleotide (NAD^+). Lactate dehydrogenase (LDH) causes lactic acid production as a terminal compound through a fermentation reaction (30). In the reaction, lactate dehydrogenase (LDH) takes off electrons from reduced form nicotinamide adenine dinucleotide (NADH) and makes nicotinamide adenine dinucleotide (NAD^+), which is directed in glycolysis process to synthesize adenosine triphosphate (ATP) (41). Although this reaction synthesizes minimal adenosine triphosphate (ATP) in comparison with the electron transfer chain (ETC), it lets cells performing physiological and biochemical activities in oxygen absence (41).

In practice, as muscles deplete oxygen, pyruvate is converted to lactic acid by lactate dehydrogenase (LDH) (39). For red blood cells (RBCs) pyruvate is no more experienced metabolism due to mitochondria lack but keeps within cytoplasm, ultimately transforming to lactate. This reactivity leads to that reduced form nicotinamide adenine dinucleotide (NADH) oxidizes to nicotinamide adenine dinucleotide (NAD^+). The presence of elevated intracellular levels of nicotinamide adenine dinucleotide (NAD) is urgent to perform the preliminary stage of glycolysis. Net adenosine triphosphate (ATP) synthesis of anaerobic glycolysis is 2 adenosine triphosphate (ATP) per glucose (Glc) molecule in comparison with oxidative phosphorylation that synthesizes 36 adenosine triphosphate (ATP) per glucose (Glc) component. Lactate dehydrogenase (LDH) has the ability in catalyzing dehydrogenation of 2-hydroxybutyrate, but it is the less preferred substrate for lactate dehydrogenase (LDH) than lactate (39).

2.3 Molecular Characteristics of Lactate Dehydrogenase

The four lactate dehydrogenase (LDH) genes are LDHA, LDHB, LDHC and LDHD (32). LDHA, LDHB and LDHC are L isomers, while LDHD is a D isomer. L isomers use or synthesize L-lactate. Human LDHA gene is placed on chromosome 11p15.4, transcription results in a protein having 332 amino acids (AAs), an estimated molecular weight of 37 kilo Dalton (kDa) and 24 splice variants; in addition, human genome has non-transcribed LDHA pseudogenes. LDHA and LDHB are believed to have arisen from transcription of a single LDHA-like LDH gene. LDHC, a testes-specific gene, is believed developed in mammals from transcription of LDHA gene after A-B transcription(32).

2.4 Elevated and Decreased Lactate Dehydrogenase Levels

Lactate dehydrogenase (LDH) enzyme is profused in renal, cardiac, hepatic and muscular tissue cells (35). Lactate dehydrogenase (LDH) enzyme levels in different tissue cells are nearly 1,500 to 5,000 times more than those present in sera (31). Hence, enzyme infiltration from even a little mass of disrupted cell elevates recognized serum efficiency of lactate dehydrogenase (LDH) to considerable range (31). Elevated lactate dehydrogenase (LDH) level was recognized in various states such as tissue injury, necrosis, hypoxia, hemolysis or malignancies (42). Higher serum lactate dehydrogenase (LDH) may be recognized following damage to any of the myriad cell types that normally express lactate dehydrogenase (LDH) (5). Conditions that can lead to increased lactate dehydrogenase (LDH) in the serum may involve liver disease, anemia, heart attack, bone fractures, muscle trauma, cancers, and infections (30). Prompt results in coronavirus disease 2019 (COVID-19) patients has proposed noticeable variations in lactate dehydrogenase (LDH) levels between patients and those with no acute infection(28). Lactate dehydrogenase (LDH) is a non-specific marker of tissue turnover, a normal metabolic path (30). In myocardial infarction (MI) the occurrence of lactate dehydrogenase (LDH) is higher than that of serum glutamic oxaloacetic transaminase (SGOT) and creatine phosphokinase (CPK)(35). The principal benefit of lactate dehydrogenase (LDH) determination is that its increase is much more prolonged, and is thus of particular worth. Initial blood specimens cannot be gained until some days following the infarctive episode. Lactate dehydrogenase (LDH) begins to elevate 12 hours after infarction, reaching peak within 48 hrs. and remains elevated for another eleven days. Elevated lactate dehydrogenase (LDH) levels are present in renal disease, liver disease,

disseminated malignant disease and particular hematological anomalies. Renal infarction or trauma may be accompanied by elevated lactate dehydrogenase (LDH) and some of patients of chronic hepatitis and nephritic syndrome may exhibit elevated lactate dehydrogenase (LDH) activity (35). Many cancers lead to a general elevation in lactate dehydrogenase (LDH) levels or an elevation in one of its isozymes (30). Hence, it is a non-specific tumor biomarker with no benefit in diagnosis of the type of malignancy (30).

2.5 Lactate Dehydrogenase as a Biomarker

The measurement of lactate dehydrogenase (LDH) clinically important because serum levels of lactate dehydrogenase (LDH) isozymes reflect tissue-specific pathological statuses (30). Lactate dehydrogenase (LDH) may be a beneficial biomarker for various tissue destructions because of its isozyme type, and its omnipresence. In case tissue destruction, cells liberate lactate dehydrogenase (LDH) in blood. According to type of tissue harm, the enzyme can continue increased for 7 days in blood. Higher lactate dehydrogenase (LDH) in serum results from tissue deterioration and happens because of noticeable cell apoptosis. Tissue destruction may be because of diseases such as acute myocardial infarction (MI), anemia, pulmonary embolism (PE), hepatitis, acute renal failure (ARF), etc. Lactate dehydrogenase (LDH) is a satisfying biomarker for disease staging (S-classification), observing disease prediction or react to therapy, and for assessing body fluids in addition to blood. The reduction in lactate dehydrogenase (LDH) amounts as a result of uptaking therapy is an indicator for good disease valuation or responding well to management in states of diseases. In condition of acute myocardial infarction (MI), LDH-1 isozyme continues increased from 2nd day to 4th day. In the same status, in liver disease, LDH-5 is increased. A considerable elevation in LDH-5 higher than LDH-4 is a sign of hepatocellular diseases. There is a notable elevation in lactate dehydrogenase (LDH) during intracranial hemorrhage. Higher than 40 U/L elevation above average levels is seen in central nervous system (CNS) lymphoma, leukemia, and metastatic cancer. More than one isoenzyme elevated levels can be marker of more than one cause of tissue disruption, as pneumonia correlated with a cardiac failure. Abnormal high levels of lactate dehydrogenase (LDH) seem associated with acute disease or multiple organ failure (MOF) (30). Lactate dehydrogenase (LDH) is the only serum biomarker of benefit for predicting metastasis of melanoma (43). In malignant diseases, growth of cancer cells utilizes oxygen higher than the

available; then, hypoxia is a prevalent consequence. Growing tumors experience lactate dehydrogenase (LDH) mediated energy release to achieve the need of haste cellular outgrowth (44). In consequence, lactate dehydrogenase (LDH) is a determined marker of metastases, particularly in the liver. Higher lactate dehydrogenase (LDH) levels have been linked to worse results in patients with other viral diseases previously (24). Precocious findings in coronavirus disease 2019 (COVID-19) patients supposed noticeable variations in lactate dehydrogenase (LDH) levels between patients and with no acute infection. Although lactate dehydrogenase (LDH) is conventionally regarded a biomarker of heart deterioration since the 1960s, anomalous levels may emerge from multiple organ harm and reduced oxygen supply with glycolysis upregulation. The acidic extracellular pH resulted from elevated lactate levels from infection and tissue deterioration provokes induction of metalloproteases and promotes macrophage mediated angiogenesis. Serious infectious diseases can result in cytokine-mediated tissue deterioration, and lactate dehydrogenase (LDH) liberation (24). Lactate dehydrogenase (LDH) has been noticed as a sign for severe prognosis in different diseases, involving cancer and infection (21). In general, lactate dehydrogenase elevation refers to tissue damage (45). Higher lactate dehydrogenase (LDH) was a widespread outcome in patients diseased with Middle East respiratory syndrome-coronavirus (MERS-CoV), avian influenza A (H7N9), and avian influenza or bird flu (H5N1) (45). Lactate dehydrogenase (LDH) was regarded as an autonomous marker of decease for individuals with severe acute respiratory syndrome (SARS) and influenza A virus subtype H1N1 infection (46-47). Lactate dehydrogenase (LDH) is elevated in acute and drastic lung destruction, and higher lactate dehydrogenase (LDH) levels are reported in other interstitial pulmonary infectious diseases (48). Lactate dehydrogenase is also a potent biomarker associated with acute respiratory distress syndrome (ARDS) mortality (45).

Deficiency of lactate dehydrogenase (LDH) is scarce and can be as a result of mutations in the LDHA gene or the LDHB gene leading to deficient LDH-A (M- subunit protein) and LDH-B (H- subunit protein) proteins, respectively. LDHA gene mutations lead to abnormal M subunit protein production which lacks binding capability to other subunits in order to produce lactate dehydrogenase (LDH) (49).

It has been observed that higher serum lactate dehydrogenase (LDH) levels are associated with poor prognosis in different diseases, particularly in tumors and inflammation (50-51). Lactate

dehydrogenase (LDH) is an immune monitoring disease valuation biomarker since its increase is prediction of negative result in immunosuppressed individuals(52). Lactate dehydrogenase (LDH) elevates synthesis of lactate, causing increase in immune-suppressing cells, involving macrophages (MΦ) and dendritic cells (DCs), and restraint of cytolytic cells, as natural killer (NK) cells and cytotoxic T-lymphocytes (CTLs)(4). Lactate dehydrogenase (LDH) is frequently triggered in accordance to T cell promotion and propagation(4). In an analysis study of a cytotoxic T lymphocytes (CTLs) antigen-4 antibody which could promote T-cell efficiency and propagation, finding revealed elevation in lactate dehydrogenase (LDH) level was a hallmark of an indigent result, hence, assuring hindering impact of lactate dehydrogenase (LDH) on cytotoxic T lymphocytes (CTLs) (53). Moreover, CD4⁺ T cells secrete little interferon-gamma (IFN-γ) in lactate dehydrogenase (LDH) absence, indicating a stringent role for lactate dehydrogenase (LDH) in inducing T cell reactions(4). Modification in lactate changed the inflammatory responding in macrophages (MΦ)(54). It was realized that suppression of lactate dehydrogenase (LDH) has anti-inflammatory impacts attributed to decreased regulation of some inflammatory interfaces involving cytokines and nitric oxide (NO) (54). In addition, a study found noticeable correlations were detected between lactate dehydrogenase (LDH) and cytokines/chemokines, thus, lactate dehydrogenase (LDH) may be a biomarker of interest for its role in assisting the physician in deduction to admit to hospital a tot with bronchiolitis(55). Poggiali *et al.* (2020) recorded strongest findings in their study which were the correlations between lactate dehydrogenase (LDH) and C-reactive protein (CRP) serum levels with PaO₂/FiO₂ ratio [the ratio of arterial oxygen partial pressure (PaO₂ in mmHg) to fractional inspired oxygen (FiO₂ expressed as a fraction, not a percentage)] values (56). Depending upon multivariate analytical statistics, these connections did not affect by sex, age, neutrophils, lymphocytes, platelets count, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatine kinase (CK) serum levels. Further, lactate dehydrogenase (LDH) associate with C-reactive protein (CRP) and another inflammatory indicators proposing a probable correlation between tissue destruction and the infectious state (56). In other words, lactate dehydrogenase (LDH) is a sign of an acute or chronic tissue harm and is deemed as inflammatory indicator(57). C-reactive protein (CRP) is a notable marker of acute inflammation(57). In addition, C-reactive protein (CRP) is a liver protein adjusted by interleukin-6 (IL-6) and interleukin-1 (IL-1)(45).

Lactate dehydrogenase (LDH) procedure is based on the level of lactate dehydrogenase (LDH) found in the serum that infiltrated from cells as a result of destruction (30). The inducing characteristic of lactate dehydrogenase (LDH) causing reversible oxidation of L-lactate to pyruvate, boosted by hydrogen acceptor, nicotinamide adenine dinucleotide (NAD^+), is employed as a ground for measuring lactate dehydrogenase (LDH) efficiency. Clinical diagnostic laboratories evaluate percent of synthesis of reduced nicotinamide adenine dinucleotide (NADH) that alters optical density of specimen evaluated spectrophotometrically at 340 nm. Transformation of pyruvate to lactate or inverse reaction of oxidation of L-lactate to pyruvate can be predicted by spectrophotometry. Lactate dehydrogenase (LDH) efficacy can be quantified in different samples such as plasma, serum, tissue, cells, and in the culture medium. There should be handling precaution when serum and plasma are the samples because hemolysis can result in an artefactual elevation in the enzyme levels attributed to its liberation from destructed red blood cells (RBCs) (30).

Representatively, normal average of lactate dehydrogenase (LDH) ranges from 140 to 280 U/L (30). Clinical explanation relies on disease presentations of infected individual. Serum has a higher level of lactate dehydrogenase (LDH) in comparison with plasma because lactate dehydrogenation (LDH) liberates during coagulating activity. Lactate dehydrogenase (LDH) efficacy also elevates in exhausting practice to produce lactic acid under straight physiological statuses. Lactate dehydrogenase (LDH) assay is influenced by administered therapy, which could intervene with precise measurement of lactate dehydrogenase (LDH). Presence of elevated levels of vitamin C may cause drop in lactate dehydrogenase (LDH) levels reading. Anesthetics, aspirin, alcohols, particular narcotics, and procainamide can elevate lactate dehydrogenase (LDH) quantity. Lactate dehydrogenase (LDH) assay may just show an increased level of one or more patterns of isozymes. Hepatic diseases, renal diseases, muscle injury, trauma, cardiac failure, particular infections, pancreatitis, malignancy, and anemia are among health situations that may cause elevation in serum lactate dehydrogenase (LDH) levels. Further, the lactate dehydrogenase (LDH) level changes with age, infants and young children commonly have much elevated physical lactate dehydrogenase (LDH) levels in comparison with older children and adults. Newborns' physical average ranges from 135 to 750 U/L (units/L), children up to 12 months have 180 to 435 U/L and above 18 years of age have a physical average ranging from 122 to 222 U/L (as indicated by Mayo Clinic Labs) (30).

Aside from measuring lactate dehydrogenase (LDH) level in samples, lactate dehydrogenase (LDH) isozymes measurement also offer the assessment of the type, location, and severity of tissue deterioration (30). Lactate dehydrogenase (LDH) isozymes identification depends on electrophoretic mobility shift. Different subunit structure relates a variation in the net charges and hence varied migration in an electric field. A notable secession style of lactate dehydrogenase (LDH) isozymes is gained in a pH 8.6 buffered solution. In an ideal lactate dehydrogenase (LDH) isozyme electrophoretic pattern, LDH-1 gets about as a rapid band, followed by LDH-2, LDH-3, LDH-4, and LDH-5 being the indolent band. The average serum proportion of LDH-1 (4H) is 30.4 to 36.4%, LDH-2 (3H1M) is 30.4 to 36.4%, LDH-3 (2H2M) is 19.2 to 24.8%, LDH-4 (1H3M) is 9.6 to 15.6%, and LDH-5 (4M) is 5.5 to 12.7%. In addition, lactate dehydrogenase (LDH) efficacy is influenced by hemolysis of blood specimen. As red blood cells (RBC) have lactate dehydrogenase (LDH), hemolysis leads to an artifactual rise causing false-positive elevated outcomes. Cell necrosis may also lead to elevated serum level, and its omnipresent apportionment through tissues entails an intense obstruction to its benefit clinically as a biomarker (30). Serum lactate dehydrogenase (LDH) is routinely tested in various diseases clinically (11). Abnormal lactate dehydrogenase (LDH) levels can occur as a result of multiple organ damage and reduced oxygen supply with high regulation of glycolysis (24). Severe infectious diseases may develop cytokine-mediated tissue disrupt and lactate dehydrogenase (LDH) liberate (24). Tao *et al.* (2018) showed that lactate dehydrogenase (LDH) was responsible of decease in patients with community acquired pneumonia (CAP) resulted from viral infections (58). Lactate dehydrogenase (LDH) is ascertained as a disease predicting factor with higher reliability in diseases including multiple organ harms such as acute heart failure (AHF) and severe acute pancreatitis (AP) (59-60). Studies have demonstrated that patients with severe coronavirus disease 2019 (COVID-19) have higher serum lactate dehydrogenase (LDH) levels (61-62). The quantification of serum levels of lactate dehydrogenase (LDH) isozymes indicate tissue-specific pathological environments (30). Thus, lactate dehydrogenase (LDH) can be utilized as a biomarker for various tissue diseases attributing to its isozyme pattern, and its everywhere finding. Reduction in lactate dehydrogenase (LDH) levels during therapy administration is referring to well prognosis and/or notable response to management in states such as acute myocardial infarction (MI) or hepatic injury. In acute myocardial infarction (MI), LDH-1 isozyme continues raised from 2nd day to upward to 4th day. Hepatic injury exhibits raised

LDH-5 level. Lactate dehydrogenase (LDH) elevates during surge in serous body fluids such as pericardial and peritoneal fluids. Hence, it functions to represent surge. In cerebrospinal (CSF) fluid, lactate dehydrogenase (LDH) becomes higher in bacterial meningitis, while it is recognized to be normal in viral meningitis. The ratio of fluid lactate dehydrogenase (LDH) compared to the upper limit of normal serum lactate dehydrogenase (LDH) (> 0.6) refers to an inflammatory process, and later exudate. Lactate dehydrogenase (LDH) is an essential prognostic factor since diseased individuals with elevated lactate dehydrogenase (LDH) have decreased subsistence proportions. In addition, lactate dehydrogenase (LDH) levels function to estimate metastasis in uveal melanoma (30). Lactate dehydrogenase (LDH) expresses a better relation with tyrosine kinase (TK) production in tumors (63). Lactate dehydrogenase also exhibits a potent therapeutic goal for illnesses such as malaria and cancer (30). Lactate dehydrogenase (LDH) isoform expressed by *Plasmodium falciparum*, the malarial parasite, is an essential enzyme for creation of energy in this pathogen (30). These malarial pathogens lack citric acid cycle for adenosine triphosphate (ATP) synthesis, anaerobic glycolytic pathway functions as energy originator (64). The inhibitors of *Plasmodium falciparum* LDH are pointed towards the parasite and will electically settle the parasite (64). Most invading tumors suffer a metabolic turning (Warburg effect) from oxidative phosphorylation to higher anaerobic glycolytic pathway (30). This turn is incident through upward regulation of LDH-5 (also called LDH-A), the isoform commonly found in muscles and liver (65). So, prevention of LDH-5 can particularly attack the locus of both progress and invasion of tumor (65). It is indicated that selecting LDHA genes or LDH-5 can be employed as a cancer metabolic management (64). LDHA gene mutation almost impacts skeletal muscles since skeletal lactate dehydrogenase (LDH) has all M-subunits (30). Absence of functional subunit decreases quantity of enzyme produced in all other tissues. This leads an ineffectual glycogen collapse. LDHA gene disorder is also called glycogen storage disease XI (30). Non-available of enough energy, particularly to muscle cells, leads to muscle impairment and muscle collapse (rhabdomyolysis) (66). LDHA deficiency individuals may suffer from skin rashes of differing gravity (30). LDHB gene mutations impact heart muscle potentially because heart lactate dehydrogenase (LDH) is consists of all four H-subunits. In heart muscle, the involuntary muscle activity is fueled by the transformation of lactate to pyruvate through lactate dehydrogenase. Such environments result in a decreased lactate dehydrogenase (LDH) efficacy in heart muscle of LDHB deficient individuals.

Of interest, no apparent phenotype, signs, or presentations are seen in such sick individuals. Both LDHA and LDHB gene mutations have indicated relation in tumorigenesis (30).

2.6 Lactate Dehydrogenase Levels in COVID-19 Infection

Lactate dehydrogenase (LDH) release is induced by necrosis of the cell membrane, suggesting viral infection or lung damage, such as the pneumonia stimulated by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)(29). In general, lactate dehydrogenase (LDH) is a signal of an acute or chronic tissue destruction and is regarded as inflammatory biomarker (57). When lactate dehydrogenase (LDH) levels are correlated with computed tomography (CT) scan, noticeably elevated levels reflect pneumonia severity(67). There is a satisfactory proof binding lactate dehydrogenase(LDH) levels to the development of coronavirus disease 2019 (COVID-19)(68). In a study done by Shi *et al.* (2020) disease sufferers were ranged by level of lactate dehydrogenase (LDH) and stage of life (45). In comparison with diseased individuals who had normal lactate dehydrogenase (LDH) levels at hospital administration, cases with lactate dehydrogenase (LDH) higher than normal average were at considerably higher risk of sickness progression. Shi *et al.* (2020) finding of elevated lactate dehydrogenase (LDH) in the early phase of severe coronavirus disease 2019 (COVID-19) patients proposed probable subclinical tissue damage (45). A multi-center article comprising 1099 sick persons administered boosting proof associating range of tissue destruction and inflammation with elevating lactate dehydrogenase (LDH) levels (69). The acidic extracellular pH as a result of elevated lactate from infection and tissue damage induces activation of metalloproteases and improves macrophage (MΦ) mediated angiogenesis (24). Acute infectious diseases may develop cytokine-mediated tissue collapse and lactate dehydrogenase (LDH) liberation (24). A study showed that there was a considerable increase in lactate dehydrogenase (LDH) amounts among recalcitrant coronavirus disease 2019 (COVID-19) individuals(62). There is rising trust in using lactate dehydrogenase (LDH) enzyme as indicator for measuring intensity of coronavirus disease 2019 (COVID-19)(29). A literature revealed noticeably increased levels of lactate dehydrogenase (LDH) in intensive care unit (ICU) patients than non-intensive care unit (non-ICU) patients (70). A elevated levels of lactate dehydrogenase (LDH) continued in the intensive care unit(ICU) patients number of days post-admission, lactate dehydrogenase (LDH) can be considered an estimating biomarker of severe disease (70). Fan *et al.* (2020) in their series of coronavirus

disease 2019 (COVID-19) patients from Singapore described absolute lymphocyte count and lactate dehydrogenase (LDH) as discriminators between intensive care unit (ICU) and non-intensive care unit (non-ICU) patients (71). It is expected that rise in lactate dehydrogenase (LDH) is common in coronavirus disease 2019 (COVID-19) patients in the intensive care unit (ICU) setting and shows a poor result (5). Higher lactate dehydrogenase(LDH) level was recorded to be risk factors linked to in-hospital decease in coronavirus disease 2019 (COVID-19) (21).

Coronavirus disease 2019 (COVID-19) is an illness that can progress to multiple organ damage including heart, liver and kidney destructions(23). Li *et al.* (2020) described that high serum lactate dehydrogenase (LDH) level was an independent indicator for foresee severity and mortality in patients with coronavirus disease 2019 (COVID-19) (11). In a study, as proposed by comparison of laboratory indicators, there were considerable variations in the levels of white blood cells (WBC), neutrophils, lymphocytes, C-reactive protein (CRP), fibrinogen, D-dimer (DD), creatine kinase (CK) and lactate dehydrogenase (LDH) between non-severe and severe groups. Recognizably, lactate dehydrogenase (LDH) exerted a potent correlation with the other indexes by Pearson correlation analysis, which supposed that lactate dehydrogenase (LDH) was a considerable factor combined with the severity of patients with coronavirus disease 2019 (COVID-19). When the body undergoes acute hypoxia or inflammation, the serum lactate dehydrogenase (LDH) level will elevate noticeably. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) infection, majorly includes in the lungs, as well as other tissues and organs, resulting in hypoxia, thrombogenesis, inflammation and organ injury (11).

The pooled analysis of a study conducted by Henry *et al.* (2020) showed an association between higher lactate dehydrogenase (LDH) levels and worst results in ill individuals with coronavirus disease 2019 (COVID-19) (24). In particular, there was a N6-double elevation in odds of intense infection and a N16-double elevation in odds of death rate in infected individuals with higher lactate dehydrogenase (LDH) (24). Poggiali *et al.* (2020) recorded that lactate dehydrogenase (LDH) is associated with respiratory function (PaO_2/FiO_2) and can be suggesting respiratory collapse in coronavirus disease 2019 (COVID-19) infected individuals (72). Han *et al.* (2020) interpreted that lactate dehydrogenase (LDH) could be regarded as a potent factor for

initial description of lung disease and severe coronavirus disease 2019 (COVID-19) infected individuals (4). Severe infectious diseases may develop cytokine-mediated tissue damage and lactate dehydrogenase (LDH) secretion (73). Since lactate dehydrogenase (LDH) is found in lung tissue (isozyme 3), sic individuals with severe coronavirus disease 2019 (COVID-19) infections may be proposed to liberate higher quantities of lactate dehydrogenase (LDH) in the circulation, as a stringent form of interstitial pneumonia, frequently developing to acute respiratory distress syndrome (ARDS), is the lineament of this infection. Raised lactate dehydrogenase (LDH) level in coronavirus disease 2019 (COVID-19) in severe conditions supposed that lactate dehydrogenase (LDH) may be related to lung injury and tissue deterioration (21). It is the biomarker that most potently associated with acute respiratory distress syndrome (ARDS) mortality (45). Yu *et al.* (2020) showed that high lactate dehydrogenase (LDH) level was an independent risk factor associated with acute respiratory distress syndrome (ARDS) among coronavirus disease 2019 (COVID-19) infected individuals (2). Moreover, Yu *et al.* (2020) administered that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infected patients who progressed acute respiratory distress syndrome (ARDS) were older and had elevated systolic blood pressure (SBP), serum creatinine, and lactate dehydrogenase (LDH) levels. This group of individuals also had decreased lymphocyte counts. Multivariate analysis presumed that only elevated systolic blood pressure (SBP) level and raised lactate dehydrogenase (LDH) level were independent risk factors related to acute respiratory distress syndrome (ARDS) among coronavirus disease 2019 (COVID-19) infected individuals (2). Among the risk factors, Han *et al.* (2020) searched in their study, they unexpectedly discovered that lactate dehydrogenase (LDH) hold the utmost positive correlation between both pneumonia severity index (PSI) and computed tomography (CT) score. The pneumonia severity index (PSI) or Pneumonia Patient Outcomes Research Team score (PORT Score) is described as a clinical suggestion rule that medical practitioners can use to calculate the possibility of morbidity and mortality among infected individuals with community acquired pneumonia (CAP) (74). It was demonstrated a potent correlation between lactate dehydrogenase (LDH) with lung disruption as well as coronavirus disease 2019 (COVID-19) severity. Lactate dehydrogenase (LDH) is identified to be elevated in both acute and severe pulmonary destruction, and higher lactate dehydrogenase (LDH) is been observed in other interstitial pulmonary infectious diseases (56). In a significant literature, acute respiratory distress syndrome (ARDS) in coronavirus disease

2019(COVID-19) infected individuals has been attributed a systemic hyper-inflammation or cytokine storm, supported by interleukin-6 (IL-6) and interleukin-1 (IL-1) rise (75). In coronavirus disease 2019 (COVID-19) affected individuals, lactate dehydrogenase (LDH) and C-reactive protein (CRP) could indicate lung destruction and could reflect the respiratory distress subsequent to the anomalous inflammatory condition. A small cohort study of 27 patients, C-reactive protein (CRP) associated with computed tomography (CT) outcomes and led to noticeably elevated at the initial phase of severe coronavirus disease 2019 (COVID-19) before modifications in the computed tomography (CT) score (76). Chest computed tomography (CT) possesses a crucial role for diagnosis and prediction of adversity of lung disease complication in coronavirus disease 2019 (COVID-19) pneumonia (56). Currently, computed tomography (CT) scans are utilized to evaluate lung damage, and computed tomography (CT) results can be beneficial to suggest pernicious result (56).

Han *et al.* (2020) found that lactate dehydrogenase (LDH) was positively associated with C-reactive protein (CRP), aspartate aminotransferase (AST), brain natriuretic peptide (BNP), and cardiac troponin I (cTnI), while negatively associated with lymphocyte cells and its subsets, comprising CD3⁺, CD4⁺ and CD8⁺ T cells (4). This administered the finding that the myocardial and liver injury caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) could be related to the forthright destruction of the virus to objected organs, but not of hypoxia triggered by lung disease. Lactate dehydrogenase (LDH) levels are increased in thrombotic microangiopathy, which is linked to renal failure and myocardial injury (77-78).

As the increasing experience with coronavirus disease 2019 (COVID-19) in the world, numerous research articles found that lactate dehydrogenase (LDH) was related to the adversity and weak outcomes of coronavirus disease 2019 (COVID-19) (23). Shi *et al.* (2020) revealed that elevated lactate dehydrogenase (LDH) level was an autonomous risk factor for the arousal in moderate coronavirus disease 2019 (COVID-19) affected individuals (79). A study revealed correlation of lactate dehydrogenase (LDH) with the in-hospital death rate in grave or stringent patients with coronavirus disease 2019 (COVID-19) and referred to that lactate dehydrogenase (LDH) level was an autonomous risk factor of in-hospital death rate (23). It was predicted that physicians need to implement more antagonistic therapies to patients with lactate dehydrogenase (LDH) ≥ 353.5 U/L (23).

The strongest findings of a study achieved by Poggiali *et al.* (2020) were the correlations between lactate dehydrogenase (LDH) and C-reactive protein (CRP) serum levels with the ratio of arterial oxygen partial pressure (PaO₂ in mmHg) to fractional inspired oxygen (FiO₂ expressed as a fraction, not a percentage) (PaO₂/ FiO₂) (56). In this study, these relations were not affected by sex, age, neutrophils, lymphocytes, platelets count, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine kinase (CK) serum levels. In addition, lactate dehydrogenase (LDH) correlates with C-reactive protein (CRP) and other inflammatory biomarkers hinting a potent relationship between tissue deterioration and the infectious stage (56).

Elevation of lactate dehydrogenase (LDH), the immune-related indicator, might be identified as an estimating indicator, that mirrored a weak disease prediction in severe coronavirus disease 2019 (COVID-19) affected individuals (4).

Han *et al.* (2020) made a comparison for lactate dehydrogenase (LDH) with other disease predicting indicators involving C-reactive protein (CRP), lymphocyte and aspartate aminotransferase (AST) in estimating severe coronavirus disease 2019 (COVID-19) cases in patients with different levels of coronavirus disease 2019 (COVID-19) gravity and indicated that lactate dehydrogenase (LDH) had higher reliability than C-reactive protein (CRP) and lymphocyte in assessing the gravity (4). However, Dong *et al.* (2020) demonstrated that lactate dehydrogenase (LDH) had elevated disease predicting reliability than lymphocyte and a comparable reliability as C-reactive protein (CRP) for estimating in-hospital death rate in serious and stringent ill infected individuals with coronavirus disease 2019 (COVID-19) (23).

A meta-analysis accomplished by Zhang *et al.* (2020) on patients with coronavirus disease 2019 (COVID-19) infections showed elevated C-reactive protein (CRP), lymphopenia, and raised lactate dehydrogenase (LDH) in seven studies (80). The findings of this meta-analysis demonstrated that elevated C-reactive protein (CRP), lymphopenia, and higher lactate dehydrogenase (LDH) levels were significantly associated with adverse conditions of coronavirus disease 2019 (COVID-19). The numbers of CD45⁺ lymphocytes, CD3⁺ lymphocytes, CD4⁺ T cells, CD8⁺ T cells, and CD19⁺ B cells were noticeably decreased in coronavirus disease 2019 (COVID-19) affected individuals, and the reduction was more notable in adverse cases than in non-adverse ones. In

addition, C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels were considerably higher in severe patients than in non-severe patients. It was also demonstrated that the lactate dehydrogenase (LDH) level on hospital administering negatively linked with subsistence days (80). Zhou *et al.*(2020) reached to a finding that the rate of lymphopenia in the non-susistent group was higher than that in subsistent group, and the percent of elevated lactate dehydrogenase(LDH) in non-subsistent group was notably more than that in subsistent group (81).

Yuan *et al.* (2020) studydescribed the changes of several immune cell types and serum biochemical factors during hospitalization in 94 discharged patients with coronavirus disease 2019 (COVID19)(82). Theypresented that the decline of lactate dehydrogenase (LDH) and creatine kinase (CK) was associated with the elimination of viral messenger ribonucleic acid (mRNA), particularly the serum lactate dehydrogenase (LDH) and creatine kinase (CK) level in viral messenger ribonucleic acid(mRNA) positive patients, predicting that constitutive reduction of lactate dehydrogenase (LDH) or creatine kinase (CK) levels possibly suggest an appropriate response to courseof coronavirus disease 2019 (COVID-19) infected individuals (82).

Theoretically, higher serum lactate dehydrogenase (LDH) is a potent laboratory indicator for assessing coronavirus disease 2019(COVID19)(11). Higher serum lactate dehydrogenase (LDH) as an autonomous risk factor for coronavirus disease 2019 (COVID-19) is the major conclusion of a valuable research article (11). In addition, in multivariate analysis, raised serum lactate dehydrogenase (LDH) remained an independent risk factor for coronavirus disease 2019 (COVID-19)gravity and death rate. On the same, anincreasing number of studies indicated that increased lactate dehydrogenase(LDH)level was correlated with recognizably increased death rate in patients with coronavirus disease 2019 (COVID-19)(23). Many studies throughcoronavirus disease 2019 (COVID-19) pandemic mentioned elevated lactate dehydrogenase (LDH) in severe or deceased individuals, particularly in patientsincluding cardiac injury (83).

3.Conclusions

There is noticeable proof of how the levels of lactate dehydrogenase (LDH) may alter according to gravity of coronavirus disease 2019 (COVID-19) infection. There is a significant relationship between elevated levels of lactate dehydrogenase (LDH) and coronavirus disease 2019 (COVID-19) severity and mortality. Thus, measurement of lactate dehydrogenase levels has the potential to be used as an early biomarker to improve the treatment of coronavirus disease 2019 (COVID-19) patients, by identification of high-risk individuals and suitable allocation of healthcare resources in the pandemic. Measurement of lactate dehydrogenase (LDH) levels can improve prognosis and decrease the mortality rates.

4. References

- 1-Wu T.;Zuo Z.; Kang S.; Jiang L.; Luo X.; Xia Z.; Liu J.; Xiao X.; Ye M.; Deng M. (2020). Multi-organ dysfunction in patients with COVID-19: a systematic review and meta-analysis. *Aging and Disease*, 11(4):874-894. <http://dx.doi.org/10.14336/AD.2020.0520>.
- 2-Yu T.; Cai S.; Zheng Z.; Cai X.; Liu Y.; Yin S.; Peng J.; Xu X. (2020). Association between clinical manifestations and prognosis in patients with COVID-19. *Clinical Therapeutics*, 42(6):964-972. <https://doi.org/10.1016/j.clinther.2020.04.009>.
- 3-Yuki K.; Fujiogi M.; Koutsogiannaki S. (2020). COVID-19 pathophysiology: a review. Elsevier. *Clinical Immunology* 215 (2020) 108427. <https://doi.org/10.1016/j.clim.2020.108427>.
- 4-Han Y.; Zhang H.; Mu S.; Wei W.; Jin C.; Xue Y.; Tong C.; Zha Y.; Song Z.; Gu G. (2020). Lactate dehydrogenase, a risk factor of severe COVID-19 patients. medRxiv The Preprint Server For Health Sciences. doi:<https://doi.org/10.1101/2020.03.24.20040162>.
- 5-Frater J.; Zini G.; d'Onofrio G.; Rogers H. (2020). COVID-19 and the clinical hematology laboratory. Wiley. *International Journal of Laboratory Hematology*, 42(Suppl.1):11-18. DOI:10.1111/ijlh.13229.
- 6-Harapan H.; Itoh N.; Yufika A.; Winardi W.; Keam S.; Te H.; Megawati D.; Hayati Z.; Wagner A.; Mudatsir M. (2020). Coronavirus disease 2019 (COVID-19): a literature review. Elsevier. *Journal of Infection and Public Health*, 13:667-673. <https://doi.org/10.1016/j.jiph.2020.03.019>.

7-Lotfi M.; Rezaei N. (2020). SARS-CoV-2: a comprehensive review from pathogenicity of the virus to clinical consequences. Wiley. *Journal of Medical Virology*, 92:1864-1874. DOI:[10.1002/jmv.26123](https://doi.org/10.1002/jmv.26123).

8-Khadka S.; Saeed H.; Bajgain Y.; Shahi J.; Yadav T.; Gupta R. (2020). Different modes of transmission and containment strategies for COVID-19. *Europasian J of Med Sci*, 2 (spec.issue).

9-Liu Z.; Xiao X.; Wei X.; Li J.; Yang J.; Tan H.; Zhu J.; Zhang Q.; Wu J.; Liu L. (2020). Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. *J Med Virol*, 92(10):1777-1784. DOI:[10.1002/jmv.25726](https://doi.org/10.1002/jmv.25726).

10-Yu WB.; Tang GD.; Zhang L.; Corlett R. (2020). Decoding the evolution and transmissions of the novel pneumonia coronavirus (SARS-CoV-2/HCoV-19) using whole genomic data. *ZR Zoological Research*, 41(3):247-257. doi: [10.24272/j.issn.2095-8137.2020.022](https://doi.org/10.24272/j.issn.2095-8137.2020.022).

11-Li C.; Ye J.; Chen Q.; Hu W.; Wang L.; Fan Y.; Lu Z.; Chen J.; Chen Z.; Chen S.; Tong J.; Xiao W.; Mei J.; Lu H. (2020). Elevated lactate dehydrogenase (LDH) level as an independent risk factor for the severity and mortality of COVID-19. *Aging*, 12(15):15670-15681.

12-Pastorino B.; Touret F.; Gilles M.; de Lamballerie X.; Charrel RN. (2020). Prolonged viability of SARS-CoV-2 in fomites. OSFPREPRINTS. <https://doi.org/10.31219/osf.io/7etga> .

13-Khadka S.; Hashmi FK.; Usman M. (2020). Preventing COVID-19 in low- and middle income countries. *Drugs Ther Perspect*,36(6):250-252. <https://doi.org/10.1007/s40267-020-00728-8>.

14-Qu G.; Li X.; Hu L.; Jiang G. (2020). An Imperative Need for Research on the Role of Environmental Factors in Transmission of Novel Coronavirus (COVID-19). *Environ Sci Technol*, 54(7):3730-3732. <https://doi.org/10.1021/acs.est.0c01102> .

15-Ong SWX.; Tan YK.; Chia PY.; Lee TH.; Ng OT.; Wong MSY.; Marimuthu K. (2020). Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. *JAMA*,323(16):1610-1612. doi:[10.1001/jama.2020.3227](https://doi.org/10.1001/jama.2020.3227).

16-Li Q.; Guan X.; Wu P.; Wang X.; Zhou L.; Tong Y.; Ren R.; Leung K.; Lau E.; Wong J.; Xing X.; Xiang N.; Wu Y.; Li C.; Chen Q.; Li D.; Liu T.; Zhao J.; Liu M.; Tu W.; Chen C.; Jin L.; Yang R.; Wang Q.; Zhou S.; Wang R.; Liu H.; Luo Y.; Liu Y.; Shao G.; Li H.; Tao Z.; Yang Y.; Deng Z.; Liu B.; Ma Z.; Zhang Y.; Shi G.; Lam T.; Wu J.; Gao G.; Cowling B.; Yang B.; Leung G.; Feng Z. (2020). Early transmissions dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*, 382:1199-1207. DOI: 10.1056/NEJMoa2001316.

17-Fenzia C.; Biasin M.; Cetin I.; Vergani P.; Mileto D.; Spinillo A.; Gismondo M.; Perotti F.; Callegari C.; Mancon A.; Cammarata S.; Beretta I.; Nebuloni M.; Trabattoni D.; Clerici M.; Savasi V. (2020). Analysis of SARS-CoV-2 vertical transmission during pregnancy. *Nature Communications*, 11:5128. <https://doi.org/10.1038/s41467-020-18933-4>.

18-Huang C.; Wang Y.; Li X.; Ren L.; Zhao J.; Hu Y.; Zhang L.; Fan G.; Xu J.; Gu X.; Cheng Z.; Yu T.; Xia J.; Wei Y.; Wu W.; Xie X.; Yin W.; Li H.; Liu M.; Xiao Y.; Gao H.; Guo L.; Xie J.; Wang G.; Jiang R.; Gao Z.; Jin Q.; Wang J.; Cao B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223):497-506. [https://doi.org/10.1016/s0140-6736\(20\)30183-5](https://doi.org/10.1016/s0140-6736(20)30183-5).

19-Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B.; Xiang H.; Cheng Z.; Xiong Y.; Zhao Y.; Wang X.; Peng Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*, 323(11):1061-1069. doi:10.1001/jama.2020.1585.

20-Zhou F.; Yu T.; Du R.; Fan G.; Liu Y.; Liu Z.; Xiang J.; Wang Y.; Song B.; Gu X.; Guan L.; Wei Y.; Li H.; Wu X.; Xu J.; Tu S.; Zhang Y.; Chen H.; Cao B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 395(10229):1054-1062. doi: [10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).

21-Li X.; Xu S.; Yu M.; Wang K.; Tao Y.; Zhou Y.; Shi J.; Zhou M.; Wu B.; Yang Z.; Zhang C.; Yue J.; Zhang Z.; Renz H.; Liu X.; Xie J.; Xie M.; Zhao J. (2020). Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol*, 146(1):110-118. <https://doi.org/10.1016/j.jaci.2020.04.006>.

- 22-Chen N.; Zhou M.; Dong X.; Qu J.; Gong F.; Han Y.; Qiu Y.; Wang J.; Liu Y.; Wei Y.; Xia J.; Yu T.; Zhang X.; Zhang L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, 395(10223):507-513. [https://doi.org/10.1016/s0140-6736\(20\)30211-7](https://doi.org/10.1016/s0140-6736(20)30211-7).
- 23-Dong X.; Sun L.; Li Y. (2020). Prognostic value of lactate dehydrogenase for in-hospital mortality in severe and critically ill patients with COVID-19. *International Journal of Medical Sciences*, 17(14):2225-2231. doi:10.7150/igms.47604.
- 24-Henry B.; Aggarwal G.; Wong J.; Benoit S.; Vikse J.; Plebani M.; Lippi G. (2020). Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. *American Journal of Emergency Medicine*, 38:1722-1726. <https://doi.org/10.1016/jajem2020.05.073>.
- 25-Liu KC.; Xu P.; Lv WF.; Qiu XH.; Yao JL.; Gu JF.; Wei W. (2020). CT manifestations of coronavirus disease 2019: a retrospective analysis of 73 cases by disease severity. *Eur J Radiol*, 126:108941. doi: [10.1016/j.ejrad.2020.108941](https://doi.org/10.1016/j.ejrad.2020.108941).
- 26-Wang D.; Hu B.; Hu C.; Zhu F.; Liu X.; Zhang J.; Wang B.; Xiang H.; Cheng Z.; Xiong Y.; Zhao Y.; Li Y.; Wang X.; Peng Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*, 323(11):1061-1069. doi:[10.1001/jama.2020.1585](https://doi.org/10.1001/jama.2020.1585).
- 27-Bai Y.; Yao L.; Wei T.; Tian F.; Jin DY.; Chen L.; Wang M. (2020). Presumed asymptomatic carrier transmission of COVID-19. *JAMA*, 323(14):1406-1407. doi:10.1001/jama.2020.2565.
- 28-Henry B.; De Olivera MHS.; Benoit S.; Plebani M.; Lippi G. (2020). Hematologic, biochemical and immune marker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID 19): a meta-analysis. *Clin Chem Lab Med*, 58(7):1021-1028. doi: [10.1515/cclm-2020-0369](https://doi.org/10.1515/cclm-2020-0369).
- 29-Kermali M.; Khalsa R.; Pillai K.; Ismail Z.; Harky A. (2020). The role of biomarkers in diagnosis of COVID-19-a systematic review. *Elsevier. Life Sciences*, 254. <https://doi.org/10.1016/j.lfs.2020.117788>.

- 30-Farhana A.; Lappin S. (2020). Biochemistry, lactate dehydrogenase (LDH). StatPearls [Internet].
- 31-Panteghini M. (2020). Lactate dehydrogenase: an old enzyme reborns a COVID-19 marker (and not only). DE GRUYTER. Clin Chem Lab Med. <https://doi.org/10.1515/cclm.2020.1062>.
- 32-Valvona C.; Fillmore H.; Nunn P.; Pilkington G. (2016). The regulation and function of lactate dehydrogenase A: therapeutic potential in brain tumor. John Wiley and Sons Ltd. Brain Pathology, 26:3-17. doi:10.1111/bpa.12299.
- 33-Shi Y.; Pinto BM. (2014). Human lactate dehydrogenase a inhibitors: a molecular dynamics investigation. PLoS ONE,9(1):e86365. <https://doi.org/10.1371/journal.pone.0086365>.
- 34-Spriet LL.; Howlett RA.; Heigenhauser GJ. (2000). An enzymatic approach to lactate production in human skeletal muscle during exercise. Med Sci Sports Exerc,32(4):756-763. DOI: 10.1097/00005768-200004000-00007.
- 35- Sagar V.; Berry V.; Chaudhary D. (2015). Diagnostic value of serum enzymes-a review on laboratory investigations. International Journl of Life Science and Pharma Research, 5(4):L-8-L-12.
- 36- Passarella S.; Schurr A. (2018). l-Lactate Transport and Metabolism in Mitochondria of Hep G2 Cells-The Cori Cycle Revisited. Front Oncol, 8:120. doi: [10.3389/fonc.2018.00120](https://doi.org/10.3389/fonc.2018.00120).
- 37-Holmes RS.; Goldberg E. (2009). Computational analyses of mammalian lactate dehydrogenases: human, mouse, opossum and platypus LDHs. Comput Biol Chem, 33(5):379-385. doi: [10.1016/j.compbiolchem.2009.07.006](https://doi.org/10.1016/j.compbiolchem.2009.07.006).
- 38-Read JA.; Winter VJ.; Eszes CM.; Sessions RB.; Brady RL. (2001). Structural basis for altered activity of M- and H-isozyme forms of human lactate dehydrogenase. Proteins,43(2):175-185. doi: [10.1002/1097-0134\(20010501\)43:2<175::aid-prot1029>3.0.co;2-#](https://doi.org/10.1002/1097-0134(20010501)43:2<175::aid-prot1029>3.0.co;2-#).
- 39-Adeva-Andany M.; López-Ojén M.; Funcasta-Calderón R.; Ameneiros-Rodríguez E.; Donapetry-García C.; Vila-Altesor M.; Rodríguez-Seijas J. (2014). Comprehensive review on lactate metabolism in human health. Mitochondrion,17:76-100. doi: [10.1016/j.mito.2014.05.007](https://doi.org/10.1016/j.mito.2014.05.007).
- 40-Overgaard M.; Rasmussen P.; Bohm AM.; Seifert T.; Brassard P.; Zaar M.; Homann P.; Evans KA.; Nielsen HB.; Secher NH. (2012). Hypoxia and exercise provoke both lactate release

and lactate oxidation by the human brain. *FASEB J*,26(7):3012-3020. <https://doi.org/10.1096/fj.11-191999> .

41- Schumann G.; Bonora R.; Ceriotti F.; Clerc-Renaud P.; Ferrero CA.; Féraud G.; Franck PF.; Gella FJ.; Hoelzel W.; Jørgensen PJ.; Kanno T.; Kessner A.; Klauke R.; Kristiansen N.; Lessinger JM.; Linsinger TP.; Misaki H.; Panteghini M.; Pauwels J.; Schimmel HG.; Vialle A.; Weidemann G.; Siekmann L. (2002). IFCC primary reference procedures for the measurement of catalytic activity concentrations of enzymes at 37 degrees C. Part 3. Reference procedure for the measurement of catalytic concentration of lactate dehydrogenase. *Clinical Chemistry and Laboratory Medicine*, 40(6):643-648.

42- Karlsson M.; Wiberg-Itzel E.; Chakkarapani E.; Blennow M.; Winbladh B.; Thoresen M. (2010). Lactate dehydrogenase predicts hypoxic ischaemic encephalopathy in newborn infants: a preliminary study. *Acta paediatrica (Oslo, Norway : 1992)*, 99(8):1139-1144.

43-Jurisc V.; Radenkovic S.; Konjevic G. (2015). The actual role of LDH as tumor marker, biochemical and clinical aspects. *Adv Exp Med Biol*, 867:115-124. DOI: 10.1007/978-94-017-7215-0_8

44- Mishra D.; Banerjee D. (2019). Lactate dehydrogenases as metabolic links between tumor and stroma in the tumor microenvironment. *Cancers (Basel)*,11(6) .DOI: 10.3390/cancers11060750.

45- Shi J.; Li Y.; Zhou X.; Zhang Q.; Ye X.; Wu Z.; Jiang X.; Yu H.; Shao L.; Ai JW.; Zhang H.; Xu B.; Sun F.; Zhang W. (2020). Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study. *BMC Medicine*, 18:168. <https://doi.org/10.1186/s12916-020-01633-7>.

46- Choi KW.; Chau TN.; Tsang O.; Tso E.; Chiu MC.; Tong WL.; Lee PO.; Ng TK.; Ng WF.; Lee KC. (2003). Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. *Ann Intern Med*,139(9): 715 –723. doi: [10.7326/0003-4819-139-9-200311040-00005](https://doi.org/10.7326/0003-4819-139-9-200311040-00005).

- 47- Xi X.; Xu Y.; Jiang L.; Li A.; Duan J.; Du B. (2010). Hospitalized adult patients with 2009 influenza A (H1N1) in Beijing, China: risk factors for hospital mortality. *BMC Infectious Diseases*, 10(1):256. doi: [10.1186/1471-2334-10-256](https://doi.org/10.1186/1471-2334-10-256).
- 48- McFadden R.; Oliphant L. (1991). Serum lactate dehydrogenase in interstitial lung disease. *Chest*, 100 (4) . <https://doi.org/10.1378/chest.100.4.1182-b> .
- 49-Monroe GR.; van Eerde AM.; Tessadori F.; Duran KJ.; Savelberg SMC.; van Alfen JC.; Terhal PA.; van der Crabben SN.; Lichtenbelt KD.; Fuchs SA.; Gerrits J.; van Roosmalen MJ.; van Gassen KL.; van Aalderen M.; Koot BG.; Oostendorp M.; Duran M.; Visser G.; de Koning TJ.; Cali F.; Bosco P.; Geleijns K.; de Sain-van der Velden MGM.; Knoers NV.; Bakkens J.; Verhoeven-Duif NM.; van Haaften G.; Jans JJ. (2019). Identification of human D lactate dehydrogenase deficiency. *Nat Commun*, 10(1):1477.
- 50- Van Wilpe S.; Koornstra R.; Den Brok M.; De Groot JW.; Blank C.; De Vries J.; Gerritsen W.; Mehra N. (2020). Lactate dehydrogenase: a marker of diminished antitumor immunity. *Oncoimmunology*, 9:1731942. <https://doi.org/10.1080/2162402X.2020.1731942>.
- 51- Pourfathi M.; Cereda M.; Chatterjee S.; Xin Y.; Kadlecsek S.; Duncan I.; Hamedani H.; Siddiqui S.; Profka H.; Ehrich J.; Ruppert K.; Rizi RR. (2018). Lung metabolism and inflammation during mechanical ventilation; an imaging approach. *Sci Rep*, 8:3525. <https://doi.org/10.1038/s41598-018-21901-0>.
- 52- 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 Journal of Emergency Medicine*,11(3):136–140. doi: [10.5847/wjem.1920-8642.2020.03.003](https://doi.org/10.5847/wjem.1920-8642.2020.03.003).
- 53- Dick J.; Lang N.; Slynko A.; Kopp-Schneider A.; Schulz C, Dimitrakopoulou-Strauss A.; Hassel J. (2016).Use of LDH and autoimmune side effects to predict response to ipilimumab treatment. *National Library of Medicine. Immunotherapy*,8(9):1033-1044. doi: [10.2217/imt-2016-0083](https://doi.org/10.2217/imt-2016-0083).

- 54-Song YJ.; Kim A.; Kim GT.; Yu HY.; Lee ES.; Park MJ.; Kim YJ.; Shim SM.; Park TS. Inhibition of lactate dehydrogenase A suppresses inflammatory response in RAW 264.7 macrophages. National Library of Medicine. Mol Med Rep, 2019;19(1):629-37.doi: [10.3892/mmr.2018.9678](https://doi.org/10.3892/mmr.2018.9678).
- 55- Laham FR.; Trott AA.; Bennett BL.; Kozinetz CA.; Jewell AM.; Garofalo RP.; Piedra P. (2010). LDH concentration in nasal-wash fluid as a biochemical predictor of bronchiolitis severity. Pediatrics,125(2):e225-233.DOI: [10.1542/peds.2009-0411](https://doi.org/10.1542/peds.2009-0411).
- 56-Poggiali E.; Zaino D.; Immovilli P.; Rovero L.; Losi G.; Dacrema A.; Nucetelli M.; Vadacca G.; Guidetti D.; Vercelli A.; Magnacavallo A.; Bernardini S.; Terracciano C. (2020). Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in COVID-19 patients. Elsevier. Clinica Chimica Acta, 509:135-138. <https://doi.org/10.1016/j.cca.2020.06.012>.
- 57- Dasgupta A.; Sepulveda J. (2019). Accurate results in the clinical laboratory. 2nd edition. Elsevier. Hardcover ISBN:9780128137765. eBook ISBN:9780128137772.
- 58-Tao RJ.; Luo XL.; Xu W.; Mao B.; Dai RX.; Li CW, Yu L.; Gu F.; Liang S.; Lu HW.; Chen KB.; Bai JW.; Ji XB.; Gu SY.; Sun XL.; Dai FH.; Jiang P.; Cao WJ.; Xu JF. (2018). Viral infection in community acquired pneumonia patients with fever: a prospective observational study. Journal of thoracic disease, 10(7):4387-4395. doi: [10.21037/jtd.2018.06.33](https://doi.org/10.21037/jtd.2018.06.33).
- 59- Yamaguchi S.; Abe M.; Arakaki T.; Arasaki O.; Shimabukuro M. (2019). Prognostic Value of Lactate Dehydrogenase for Mid-Term Mortality in Acute Decompensated Heart Failure: A Comparison to Established Biomarkers and Brain Natriuretic Peptide. Heart, lung & circulation, 29(9):1318-1327. doi: [10.1016/j.hlc.2019.11.013](https://doi.org/10.1016/j.hlc.2019.11.013).
- 60- Cui J.; Xiong J.; Zhang Y.; Peng T.; Huang M.; Lin Y.; Guo Y.; Wu H.; Wang C. (2017). Serum lactate dehydrogenase is predictive of persistent organ failure in acute pancreatitis. Journal of critical care,41:161-165. doi: [10.1016/j.jcrc.2017.05.001](https://doi.org/10.1016/j.jcrc.2017.05.001).
- 61-Zhang R.; Ouyang H.; Fu L.; Wang S.; Han J.; Huang K.; Jia M.; Song Q.; Fu Z. (2020). CT features of SARS-CoV-2 pneumonia according to clinical presentation: a retrospective analysis

of 120 consecutive patients from Wuhan city. *Eur Radiol*, 30:4417–4426. <https://doi.org/10.1007/s00330-020-06854-1>.

62-Mo P.; Xing Y.; Xiao Y.; Deng L.; Zhao Q.; Wang H.; Xiong Y.; Cheng Z.; Gao S.; Liang K.; Luo M.; Chen T.; Song S.; Ma Z.; Chen X.; Zheng R.; Cao Q.; Wang F.; Zhang Y. (2020). Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clinical Infectious Diseases*, ciaa270. <https://doi.org/10.1093/cid/ciaa270>

63- Liu J.; Chen G.; Liu Z.; Liu S.; Cai Z.; You P.; Ke Y.; Lai L.; Huang Y.; Gao H.; Zhao L.; Pelicano H.; Huang P.; McKeehan WL.; Wu CL.; Wang C.; Zhong W.; Wang F. (2018). Aberrant FGFR Tyrosine Kinase Signaling Enhances the Warburg Effect by Reprogramming LDH Isoform Expression and Activity in Prostate Cancer. *Cancer Res*, 78(16):4459-4470.

64- Granchi C.; Bertini S.; Macchia M.; Minutolo F. (2010). Inhibitors of lactate dehydrogenase isoforms and their therapeutic potentials. *Current Medicinal Chemistry*, 17(7):672-697. DOI: [10.2174/092986710790416263](https://doi.org/10.2174/092986710790416263).

65- Feng Y.; Xiong Y.; Qiao T.; Li X.; Jia L.; Han Y. (2018). Lactate dehydrogenase A: A key player in carcinogenesis and potential target in cancer therapy. *Cancer Medicine*, 7(12):6124-6136. doi: [10.1002/cam4.1820](https://doi.org/10.1002/cam4.1820).

66- Lee BJ.; Zand L.; Manek NJ.; Hsiao LL.; Babovic-Vuksanovic D.; Wylam ME.; Qian Q. (2011). Physical therapy-induced rhabdomyolysis and acute kidney injury associated with reduced activity of muscle lactate dehydrogenase A. *Arthritis Care Res (Hoboken)*, 63(12):1782-1786. doi: [10.1002/acr.20584](https://doi.org/10.1002/acr.20584).

67-Ying X.; Dong S.; Yao L.; Yanqing F.; Lingyun Z.; Xiaoming L.; Wenzhen Z. (2020). Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes. *Investigative Radiology*, 55(6):332-339. doi: [10.1097/RLI.0000000000000674](https://doi.org/10.1097/RLI.0000000000000674).

68-Ferrari D.; Motta A.; Strollo M.; Banfi G.; Locatelli M. (2020). Routine blood tests as a potential diagnostic tool for COVID-19. *Clinical Chemistry and Laboratory Medicine (CCLM)*, 58(7).DOI:<https://doi.org/10.1515/cclm-2020-0398>.

- 69- Guan WJ.; Ni ZY.; Hu Y.; Liang WH.; Ou CQ.; He JX.; Liu L.; Shan H.; Lei CL.; Hui D.; Du B.; Li LJ.; Zeng G.; Yuen KY.; Chen RC.; Tang CL.; Wang T.; Chen PY.; Xiang J.; Li SY.; Wang JL.; Liang ZJ.; Peng YX.; Wei L.; LiunY.; Hu YH.; Peng P.; Wang JM.; Liu JY.; Chen Z.; Li G.; Zheng ZJ.; Qiu SQ.; Luo J.; Ye CJ.; Zhu SY.; Zhong NS. (2020). Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*, 382:1708-1720. DOI: [10.1056/NEJMoa2002032](https://doi.org/10.1056/NEJMoa2002032).
- 70- Luo W.; Lin Y.; Yao X.; Shi Y.; Lu F.; Wang Z.; Wu D. (2020). Clinical findings of 35 cases with novel coronavirus pneumonia outside of Wuhan. *Research Square*. DOI:[10.21203/rs.3.rs-22554/v1](https://doi.org/10.21203/rs.3.rs-22554/v1).
- 71- Fan B.; Chong V.; Chan S.; Lim G.; Lim K.; Tan G.; Mucheli S.; Kuperan P.; Ong K. (2020). Hematologic parameters in patients with COVID-19 infection. *American Journal of Hematology*, 95(6):E131-E141. <https://doi.org/10.1002/ajh.25774>.
- 72-Poggiali E.; Zaino D.; Immovilli P.; Rovero L.; Losi G.; Dacrema A.; Nucetelli M.; Vadacca G.; Guidetti D.; Vercelli A.; Magnacavallo A.; Bernardini S.; Terracciano C. (2020). Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. *Elsevier. Clin Chim Acta*,509:135-138. doi: [10.1016/j.cca.2020.06.012](https://doi.org/10.1016/j.cca.2020.06.012).
- 73- Martinez-Outschoorn U.; Prisco M.; Ertel A.; Tsirigos A.; Lin Z.; Pavlides S.; Wang C.; Flomenberg N.; Knudsen E.; Howell A.; Pestell R.; Sotgia F.; Lisanti M. (2011). Ketones and lactate increase cancer cell “stemness”, driving recurrence, metastasis and poor clinical outcome in breast cancer. *Cell Cycle*, 10 (8). <https://doi.org/10.4161/cc.10.8.15330>.
- 74-Fine MJ.; Auble TE.; Yealy DM.; Hanusa BH.; Weissfeld LA.; Singer DE.; Coley CM.; Marrie TJ.; Kapoor WN. (1997). A prediction rule to identify low-risk patients with community-acquired pneumonia. *The New England Journal of Medicine*, 336 (4): 243–250. doi:[10.1056/NEJM199701233360402](https://doi.org/10.1056/NEJM199701233360402).
- 75- McGonagle D.; Sharif K.; O'Regan A.; Bridgewood C. (2020).The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev*, 19 (6). <https://doi.org/10.1016/j.autrev.2020.102537>.

- 76- Tan C.; Y. Huang Y.; Shi F.; Tan K.; Ma Q.; Chen Y.; Jiang X.; Li X. (2020). C-reactive protein correlates with CT findings and predicts severe COVID-19 early. *J Med Virol.* <https://doi.org/10.1002/jmv.25871> .
- 77- Kaplan B.; Meier-Kriesche H. (2002). Death after graft loss: an important late study end-point in kidney transplantation. *Am J Transplant*, 2(10):970-974.
- 78- Patschan D.; Witzke O.; Duhrsen U.; Erbel R.; Philipp T.; Herget-Rosenthal S. (2006). Acute myocardial infarction in thrombotic microangiopathies-clinical characteristics, risk factors and outcome. *Nephrol Dial Transplant*, 21(6):1549-1554. <https://doi.org/10.1093/ndt/gfl127> .
- 79- Shi J.; Li Y.; Zhou X.; Zhang Q.; Ye X.; Wu Z.; Jiang X.; Yu H.; Shao L.; Ai JW.; Zhang H.; Xu B.; Sun F.; Zhang W. (2020). Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study. *BMC medicine*,18(1):168. <https://doi.org/10.1186/s12916-020-01633-7>.
- 80-Zhang ZL.; Hou YL.; Li DT.; Li FZ. (2020). Laboratory findings of COVID-19: a systematic review and meta-analysis. Taylor and Francis Group. *Scandinavian Journal of Clinical and Laboratory Investigation*, 80(6):441-447. <https://doi.org/10.1080/00365513.2020.1768587>.
- 81- Zhou F.; Yu T.; Du R.; Fan G.; Liu Y.; Liu Z.; Xiang J.; Wang Y.; Song B.; Gu X.; Guan L.; Wei Y.; Li H.; Wu X.; Xu J.; Tu S.; Zhang Y.; Chen P.; Cao B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 395 (10229):1054–1062. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
- 82-Yuan J.; Zou R.; Zeng L.; Kou S.; Lan J.; Li X.; Liang Y.; Ding X.; Tan G.; Tang S.; Liu L.; Liu Y.; Pan Y.; Wang Z. (2020). The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. *Inflammation Research*, 69:599-606. <https://doi.org/10.1007/s00011-020-01342-0>.
- 83- Huang C.; Wang Y.; Li X.; Ren L.; Zhao J.; Hu Y.; Zhang L.; Fan G.; Xu J.; Gu X.; Cheng Z.; Yu T.; Xia J.; Wei Y.; Wu W.; Xie X.; Yin W.; Li H.; Liu M.; Xiao Y.; Gao H.; Guo L.; Xie J.; Wang G.; Jiang R.; Gao Z.; Jin Q.; Wang J.; Cao B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*,395(10223):497-506.doi: 10.1016/S0140-6736(20)30183-5.

UNDER PEER REVIEW