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 viacell 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 individualsin Wuhan, Hubei Province, of China(1)(2). These individualswereassured suffering from acute respiratory diseases(2).The infectionhastilydiffused from Wuhan to other places (3). The causative agent was defined as a novel coronavirus infectionon January, 2020 (1). The novel causative microbeiscalled 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 elevateddeath-ratein the interim 2002–2003(3).

Disease emerged fromsevere 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 theattempts to controlthis 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

internationalattention(4).The breakout of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was regarded to beginthrough a zoological originspreadcorrelated with shellfish emporium in Wuhan city (3). Then it was realized that individual to individualtransportassociated withtheprincipal role in the consequentdisease breakout(3).

1.1SARS-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 abetacoronavirus (β-CoV) together with two notablepathogens, 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). Resultspresumevampiresare the premierharbor of this viral agent(6). Vampires are improbable to be the animal that is a direct causativeofthe transmission ofthe 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).Aresearch studyproposed 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 snacks (9).

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded ribonucleic acid (RNA) viruses of about 30 kilo-bases (Kb) (3). Coronaviruses (CoVs) are widelycategorized into four sorts; alpha (α), beta (β), gamma (γ), and delata (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 -coronaviruses (α-CoVs) might cause asymptomatic or mildly symptomatic infectious diseases (7).

These coronaviruses (C0Vs)have four constitutional proteins; spike (S), membrane (M), envelop (E) and nucleocapsid (N) (3). Spike(S) protein is considered a primarydeterminant of coronavirus (CoV) entry into the cells of the host (7). Spike (S) proteinconsists of a glycoprotein embossing from virus surface, specifying the coronaviruses (CoVs) divergence and their host (3). Spike (S) proteinis 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 thecoronavirus (CoV) and host cell. Spike (S) protein also attaches to angiotensin converting enzyme 2 (ACE2). Angiotensin converting enzyme 2 (ACE2) expression iselevated 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) uses angiotensin-converting enzyme 2 (ACE2) to infect 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 angiotensinconverting 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 willface innate immunity (6).

1.2Modes of Transference

Role of the Seafood Market in disseminating coronavirus disease 2019 (COVID-19)maynot be clear (6). First coronavirus disease 2019(COVID-19)infected individuals were associatedwith 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 declaredproof that this beta coronavirus came from not knownplace, to the emporium where it disseminatedhastily, thoughtransfer from one individual to another may have happenedpreviously(10). Cohort of diseasedhouseindividuals and medicinal employeesassured the transmittingfindingfrom 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 anotherdeems to be

incidentthroughnearby contacts primarilythrough respiratory dropletsof coughs or sneezes from infected persons (6) (8). Fomites may be a wide source of transmission (6). Authors have foundmildvirus protein levels in dropsendowsthe microbeabilityof expanding exponentially-explaining its elevatedtransferability(12). Droplet transmission elevates with nearer contact, within 1 meter range with coronavirus disease 2019 (COVID-19)infectedindividuals, elevatingtendency of microbialentrancethroughmucous membranes of mouth, nose and eyes following exposing to probableinfectious respiratory drops (8). Although in some literature airborne transferring was not mentioned, spread by sneezing or coughing, dropscarrying coronavirus (CoV) have been airborne, and it is establishedcoronavirus (CoV)remainsanimated in that location until 3 hours (13). Coronavirus disease 2019 (COVID-19)disseminatesthrough 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-CoV2) 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)maydisseminatethrough fomites(8).Researches showed that coronavirus (CoV) can remain alive for hours out the host, such as aluminium, sterile sponges or latex surgical gloves, driftinglikelihoodoftransferthroughcontact(14). Anotable articleshowedspecimensobtained from WC utensils, were positive, indicating it a probable source of transmitting, although the negative results of specimenswere followingpurgation(15).

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) incubation period is in the interim from3 to 7 days and coronavirus disease 2019 (COVID-19) is infectious in latent interim (8). A notable research articleshowed mean incubation interim was 5.2 days(16). Incubation period can be from 19 to 24 days although case definitions usuallyregard a 14 day overture(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)showedfindingsprovided 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).

1.3Risk Factors

Coronavirus disease 2019 (COVID-19) is observedfrequently 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 complicationscan be also correlated with co-infections of bacteria and fungi (6). It is found that children are less probably to experience the diseaseand if happens exhibitmore moderatesymptoms than adult cases (6).

1.4Symptoms 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) infectioninvolve dyspnoea, chest pain, and fatigue (6). Nearly one half of the infected individualsexperience dyspnea after 1 week (2).Prevalentdisease presentationsinvolve headache, dizziness, abdominal pain, diarrhoea, nausea, and vomiting (6). It was found that about 75% infected individualscomplained 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 characteristicsexhibited by infected persons during the coronavirus disease 2019 (COVID19) pandemic are respiratory features (5).

Some infected individuals have moderatedisease presentations with no haven or not developing pneumonia and originallyheal after 1 week (2).Besides that the coronavirus disease 2019(COVID19)casesundergomoderate disease manifestations in their early phase, nearly 8 to 30% of infected individualsmightultimatelyprogressacutedisease (21). It was mentioned that the 28-day death rate of stringentpatientswasmore 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 broadlynoticed that aerobicpresentations 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 develophastily 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 mightdevelophastily (18).A study documented that some infected individualsdevelopedhastilytoacute respiratory distress syndrome (ARDS) and septic shock, which was ultimatelysucceeded by multiple organ failure and 10% of infected individualsdeceased(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), arrythmia, 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 individualsprogressed toacute respiratory distress syndrome (ARDS)in whom 11%deceased as a result ofmultiple organfailure (22). A study showed that the median period from first symptoms to development of acute respiratory distress syndrome (ARDS) was 8 days (6).Severelycoronavirus disease 2019(COVID-19)infected individualsmightbreak downhastily to experience multiple organ damage, impaired immune response, and even mortality(11). Epidemiological investigationspresented that mortalities are elevated in elder people and the occurrence of death is lessamong infected children (3).

1.5COVID-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 bothlactate dehydrogenase (LDH) and myoglobin (MB) in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infectedindividuals (1).Intensive care unit (ICU)-admitted patients experience more lab testsanomalies 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 casesobserved to have elevatedlevels of granulocyte-colony stimulating factor (GCSF), interferon gamma-induced protein 10 **(**IP-10), monocyte chemoattractant protein-1A (MCP-1A), macrophage inflammatory proteins A (MIPA), and tumor necrosis factor-alpha (TNF-α).Lactate dehydrogenase (LDH) is an interesting biomarker, primarilyashigherlactate dehydrogenase (LDH) levels have been bound todeteriorating outcomes in infected individuals with other viral diseases in the bygone(24). Findings in coronavirus disease 2019 (COVID-19)individualssupposednoticeablevariations in lactate dehydrogenase (LDH) levels between diseased individuals and with noacuteinfection(28).An increasing number of studies indicated that higherlactate dehydrogenase (LDH)level was correlated with considerablyelevated mortality rates in coronavirus disease 2019 (COVID-19) patients (23).

Coronavirus disease 2019 (COVID-19)presentationsdiffer from moderatehaven to acute respiratory distress syndrome (ARDS)tangling diagnosis, disease estimation, and disease surveillance (29). Therefore,ofimportanceisassuring a patient's status in anappropriate method. Biomarkers are quantitative measuresimplementedmedically for varioussituationsindicatingmorbidprogression. When estimating a coronavirus disease

2010(COVID-19) infected individual, biomarkers can be of benefitfor clinicians in initiatingmanagement and monitoring the disease closely. A study proposedobviousproof of the way the levels of biomarkers mightalter according to gravity of coronavirus disease 2019 (COVID-19). This isbeneficial in medical practice to conductmanagement 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 specifiedtreatment, involving antiviral therapy, organ support and intensive care unit (ICU) care, to ameliorate the prognosis (11). To date, neither a vaccine nor a particulartherapy with a assured result has been available to coronavirus disease 2019 infected cases (1).

2.Lactate Dehydrogenase

2.1Lactate Dehydrogenase Structure and Isozymes

Lactate dehydrogenase (LDH) is an intracellular enzyme presentin nearly all organs' cellsof the body (24). Lactate dehydrogenase (LDH) is a cytoplasmic enzyme broadly expressed in tissue cells involvingthe heart, liver, muscles, kidneys, lungs, and in bone marrow, and in addition,red blood cells (RBCs)havingmildlevels(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 bydistinct 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 kindscollected in tetramers of any ofmuscle (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, areeveryoneexhibitingpeculiar expression in various bodytissue cells (30). Thepeculiar expression of lactate dehydrogenase (LDH) is indicating itsnecessity as ananalytical marker for diagnosis. Isozyme LDH-1 has four heart subunits (4H) and is isfound 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 particularlyfound

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

2.2Lactate 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 atwo-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 machinerycompriseslinking of reduced form nicotinamide adenine dinucleotide (NADH) to the enzymes as aninitialstage. Abundant residues at the vigorouslocus 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 rapidlyhappens in both waysleading 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 inrejuvenating 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 thesesituations to servenecessityof 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 reversibleresponse of transforming lactate to pyruvate via Cori cycle (36).

The effectiveposition of the enzyme is in its substrate-binding pocket and holdsinduciblecrucial His-193, Asp-168, Arg-171, Thr-246, and Arg-106 (30). Lactate dehydrogenase (LDH) isozymes are allconstitutionallyquiteanalogous; but, each is withspecificvividcharacteristicscaused byvariations in charged amino acids (AAs)surrounding the effectivelocus (37).Bothlactate dehydrogenase (LDH)subunits, the M subunit and H subunit,keep the identicaleffectivelocusconstitution and the amino acids (AAs)taking part in the response (30). In the tertiary constitution, alanine (Ala) of M-chain is substuituted with glutamine (Gln) in H-chain. Alanine (Ala) is a nonpolar amino acid (AA), while glutamine (Gln) is a positively charged amino acid (AA),thusofferingvarious biochemical characteristics to these two subunits. H subunit may linkquicker but possess fivefold decreasedeffectiveactionin comparison with M-subunit. Lactate dehydrogenase A (LDHA) subunit has a net charge of $^{-}6$ and shows anelevatedinclination 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 anelevatedinclination towards lactate, leading tofavoredtransformation 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 upmainly 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 stressmayresult inabsorption of lactate, hence,boosting 60% of brain metabolism, together withparticipation of cerebral lactate oxidation up to 33% (39-40).

Lactate dehydrogenase (LDH) mitochondrial existenceisreported by manyresearches (30). L-lactate, the substrate for mL-LDH, is transferred to mitochondria through L-lactate/H symporter and L-lactate/pyruvate and L-lactate/oxaloacetate antiporters. Thereafter, mL-LDH favors oxidation of L-lactate to pyruvate in mitochondrial matrix. As cancer cells demandhigher energy,glycolysis turnshigher in cancerous cells, and mitochondrial L-lactate dehydrogenase (mL-LDH)plays a role in the 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 decreaserapidlyinintensepractice. 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 keepfunctioning by synthesizingadenine triphosphate (ATP) through nicotinamide adenine dinucleotide (NAD^+). Lactate dehydrogenase (LDH)causes lactic acid production as a terminalcompound 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 reactionsynthesizesminimaladenosine triphosphate (ATP)in comparison with the electron transfer chain (ETC), it lets cellsperforming physiological and biochemical activities in oxygen absence (41).

Inpractice, as muscles deplet oxygen, pyruvate is convertedto lactic acid by lactate dehydrogenase (LDH)(39). Forred blood cells (RBCs) pyruvate is no more experience metabolism due to mitochondria lack but keeps within cytoplasm, ultimatelytransforming to lactate. This reactivity leads to thatreduced 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 preliminarystage of glycolysis. Net adenosine triphosphate (ATP) synthesis of anaerobic glycolysis is 2 adenosine triphosphate (ATP) per glucose (Glc) molecule in comparison with oxidative phosphorylationthatsynthesizes 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).

2.3Molecular 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), anestimated 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 believeddeveloped in mammals from transcription of LDHA gene after A-B transcription(32).

2.4Elevated 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 disruptedcellselevatesrecognized serum efficiency of lactate dehydrogenase (LDH) to considerablerange (31). Elevatedlactate dehydrogenase (LDH) level was recognized in variousstates 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). Promptresults in coronavirus disease 2019 (COVID-19) patients has proposednoticeablevariations in lactate dehydrogenase (LDH) levels between patients and those with noacuteinfection(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 principalbenefit of lactate dehydrogenase (LDH) determination is that its increase is much more prolonged, and is thus of particularworth. 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 elevatedlactate dehydrogenase (LDH) and some of patients of chronic hepatitis and nephritic syndrome may exhibitelevated 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).

2.5Lactate Dehydrogenase as a Biomarker

The measurement of lactate dehydrogenase (LDH) clinicallyimportantbecause serum levels of lactate dehydrogenase (LDH) isozymes reflect tissue-specific pathological statuses (30). Lactate dehydrogenase(LDH)may be a beneficialbiomarker for various tissue destructsbecause of its isozyme type, and its omnipresence. In case tissue destruction, cells liberatelactate dehydrogenase (LDH) in blood. According to type of tissue harm, theenzyme can continueincreased for 7 days in blood. Higherlactate dehydrogenase (LDH) in serum results fromtissue deteriorationand happensbecause ofnoticeable cell apoptosis.Tissue destructionmay be because of diseases such as acute myocardial infarction (MI), anemia, pulmonary embolism (PE), hepatitis, acute renal failure (ARF), etc. Lactate dehydrogenase (LDH) isa satisfyingbiomarker for disease staging (S-classification), observingdisease prediction or react to therapy, and forassessing body fluids in addition to blood. The reduction in lactate dehydrogenase (LDH)amountsas a result of uptakingtherapy is an indicatorforgooddisease valuationorresponding well to management in statesof diseases. In condition of acute myocardial infarction (MI) , LDH-1 isozyme continuesincreased from 2^{nd} day to 4^{th} day. Inthe same status, in liver disease, LDH-5 is increased. A considerableelevation in LDH-5 higher than LDH-4 is a sign of hepatocellular diseases. There is a notableelevation 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. Abnormalhigh levels of lactate dehydrogenase (LDH)seemassociated with acute disease or multiple organ failure (MOF) (30). Lactate dehydrogenase (LDH) is the only serum biomarker of benefit for predictingmetastasis of melanoma (43). In malignant diseases, growth of cancer cells utilizes oxygen higher than the

available; then, hypoxia is aprevalent consequence. Growing tumors experiencelactate 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, particularlyin the liver. Higher lactate dehydrogenase(LDH) levels have been linkedto worse results in patients with other viral diseasespreviously(24). Precociousfindings in coronavirus disease 2019 (COVID-19) patients supposednoticeablevariations in lactate dehydrogenase (LDH) levels between patients and with noacuteinfection. Although lactate dehydrogenase (LDH)isconventionallyregarded a biomarker of heartdeterioration since the 1960s, anomalouslevelsmayemerge from multiple organ harm and reducedoxygen supply with glycolysisupregulation. The acidic extracellular pH resulted fromelevated lactate levels from infection and tissue deterioration provokesinduction of metalloproteases and promotes macrophage mediated angiogenesis. Seriousinfectious diseasescan 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 widespreadoutcome 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 autonomousmarker of decease for individuals with severe acute respiratory syndrome (SARS) and influenza A virus subtype H1N1infection (46-47). Lactate dehydrogenase (LDH)iselevatedin acute and drastic lung destruction, and higher lactate dehydrogenase(LDH)levelsare reported in other interstitial pulmonaryinfectious diseases(48). Lactate dehydrogenase is also a potent biomarker associated with acute respiratory distress syndrome (ARDS) mortality (45).

Deficiency of lactate dehydrogenase (LDH) is scarceand can be as a result of mutations in the LDHA gene or the LDHB gene leading todeficient LDH-A (M- subunit protein) and LDH-B (H-subunit protein) proteins, respectively. LDHA gene mutations lead to abnormal M subunit protein production whichlacks binding capability to other subunits in order to producelactate 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 monitoringdisease valuation biomarker since its increase is prediction of negative result in immunosuppressedindividuals(52). Lactate dehydrogenase (LDH)elevatessynthesis of lactate, causingincreasein immune-suppressing cells, involving macrophages(MΦ)and dendritic cells (DCs), and restrain of cytolytic cells, as natural killer (NK) cells and cytotoxic T-lymphocytes (CTLs)(4). Lactate dehydrogenase (LDH) is frequentlytriggeredin 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, findingrevealedelevation in lactate dehydrogenase (LDH) level was a hallmark of anindigentresult, hence,assuringhinderingimpact of lactate dehydrogenase (LDH) on cytotoxic T lymphocytes (CTLs) (53). Moreover, CD4+ T cells secretelittleinterferon-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 impactsattributed to decreased regulation of some inflammatory interfacesinvolving 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 rolein 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 connectionsdid 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 anotherinflammatoryindicatorsproposing a probablecorrelation 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)procedurestry on the level of lactate dehydrogenase (LDH)found in the serum that infiltrated from cellsas a result ofdestruction (30). The inducingcharacteristic of lactate dehydrogenase (LDH)causing reversible oxidation of L-lactate to pyruvate, boosted by hydrogen acceptor, nicotinamide adenine dinucleotide (NAD^+), is employed as a groundformeasuring lactate dehydrogenase(LDH)efficiency. Clinical diagnostic laboratories evaluatepercent of synthesis of reduced nicotinamide adenine dinucleotide (NADH) that alters optical density of specimenevaluated spectrophotometrically at 340 nm. Transformation of pyruvate to lactate or inverse reaction of oxidation of L-lactate to pyruvate can be predictedby spectrophotometry. Lactate dehydrogenase (LDH)efficacycan bequantified 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 explanationrelies ondisease presentations of infected individual. Serum has a higher level of lactate dehydrogenase (LDH)in comparison with plasma because lactate dehydrogenation (LDH)liberates during coagulatingactivity. Lactate dehydrogenase (LDH)efficacy also elevatesinexhaustingpractice to produce lactic acid under straight physiological statuses. Lactate dehydrogenase (LDH)assay is influenced by administered therapy, which could intervene with precisemeasurement of lactate dehydrogenase(LDH). Presence of elevatedlevels of vitamin C may causedrop in lactate dehydrogenase(LDH) levels reading. Anesthetics, aspirin, alcohols,particular narcotics, and procainamide canelevatelactate dehydrogenase (LDH)quantity. Lactate dehydrogenase(LDH)assay may just show an increasedlevel 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 maycauseelevation in serum lactate dehydrogenase (LDH) levels. Further, the lactate dehydrogenase(LDH) levelchanges with age, infants and young children commonly have much elevatedphysicallactate 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 averageranging from 122 to 222 U/L (as indicated by Mayo Clinic Labs) (30).

Aside frommeasuringlactate dehydrogenase(LDH) level in samples, lactate dehydrogenase (LDH) isozymes measurement also offersthe assessment of the type, location, and severity of tissue deterioration (30). Lactate dehydrogenase(LDH) isozymesidentification depends on electrophoretic mobility shift. Different subunit structurerelates a variation in the net charges and hence varied migration in an electric field. A notablesecessionstyle of lactate dehydrogenase (LDH) isozymes is gained in a pH 8.6 buffered solution. In anideallactate 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)havelactate dehydrogenase (LDH), hemolysis leads to an artifactual risecausing false-positive elevatedoutcomes. Cell necrosis may alsolead toelevated serum level, and its omnipresentapportionment through tissues entails anintenseobstruction 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 reducedoxygen 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 ofdecease in patients with community acquired pneumonia (CAP) resulted fromviral infections(58). Lactate dehydrogenase(LDH)isascertainedas a disease predicting factor with higherreliability 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 diseasesattributing to its isozyme pattern, and its everywherefinding. Reduction in lactate dehydrogenase (LDH) levels during therapy administration is referringtowell 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 continuesraised from 2^{nd} day to upward to 4^{th} 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 representsurge. 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 anessentialone prognostic factor since diseased individuals with elevatedlactate dehydrogenase (LDH) have decreasedsubsistenceproportions. In addition, lactate dehydrogenase (LDH) levels function to estimate metastasis in uveal melanoma (30). Lactate dehydrogenase (LDH)expresses a betterrelation 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 anessential enzyme for creation of energy in thispathogen (30). These malarial pathogens lack citric acid cycle for adenosine triphosphate (ATP)synthesis, anaerobic glycolytic pathwayfunctions as energyoriginator (64). The inhibitors of *Plasmodium falciparum* LDH are pointed towards the parasite and willelecticallysettle the parasite (64). Most invading tumors suffer a metabolic turning (Warburg effect) from oxidative phosphorylation to higher anaerobic glycolytic pathway (30). This turnis incident through upward regulation of LDH-5 (also called LDH-A), the isoform commonlyfound in muscles and liver (65). So, prevention of LDH-5 can particularlyattack the locus of both progress and invasion of tumor (65). It isindicated that selecting LDHA genes or LDH-5 can be employed as a cancer metabolic management(64). LDHA gene mutation almostimpacts skeletal muscles since skeletal lactate dehydrogenase (LDH) has all M-subunits (30). Absence of functional subunit decreasesquantity of enzyme produced in all other tissues. This leads an ineffectual glycogencollapse. 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 differinggravity (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 environmentsresult 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 indicatedrelation 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 asignal 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, noticeablyelevated levels reflect pneumonia severity(67).There is a satisfactoryproofbinding 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 withdiseased 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)patientsproposedprobable subclinical tissue damage (45).A multi-center articlecomprising 1099 sick personsadministeredboostingproofassociatingrange of tissue destruction and inflammation with elevatinglactate dehydrogenase (LDH) levels (69). The acidic extracellular pH as a result ofelevated lactate from infection and tissue damageinduces 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 considerableincrease in lactate dehydrogenase (LDH)amounts among recalcitrantcoronavirus disease 2019 (COVID-19)individuals(62).There is risingtrust in using lactate dehydrogenase (LDH) enzyme as indicatorfor measuring intensity of coronavirus disease 2019 (COVID-19)(29). A literaturerevealednoticeablyincreased levels of lactate dehydrogenase (LDH) in intensive care unit (ICU) patients than non-intensive care unit (non-ICU) patients (70). Aselevated levels of lactate dehydrogenase (LDH) continued in the intensive care unit(ICU) patients number of days post-admission, lactate dehydrogenase (LDH)can be considered anestimating 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 anillness that canprogress 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 considerablevariations 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 serumlactate dehydrogenase (LDH) level will elevatenoticeably. Coronavirus disease 2019 (COVID19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) infection, majorlyincludes 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 higherlactate dehydrogenase (LDH)levels and worstresults in ill individuals with coronavirus disease 2019 (COVID-19) (24). In particular, there was a N6-doubleelevation in odds of intenseinfection and a N16-doubleelevation in odds of death rate in infected individuals with higherlactate dehydrogenase (LDH) (24). Poggiali *et al*. (2020) recorded that lactate dehydrogenase (LDH)isassociated with respiratory function (PaO2/FiO2) and canbe 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 diseaseand 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 liberatehigherquantities of lactate dehydrogenase (LDH) in the circulation, as a stringent form of interstitial pneumonia, frequentlydevelopingto acute respiratory distress syndrome (ARDS), is the lineament of thisinfection . Raised lactate dehydrogenase(LDH) level in coronavirus disease 2019 (COVID-19) in severe conditionssupposed 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 progressedacute respiratory distress syndrome (ARDS) were older and had elevatedsystolic 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 toacute 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)isidentified to be elevatedin both acute and severe pulmonarydestruction, and higher lactate dehydrogenase(LDH)is been observed in other interstitial pulmonaryinfectious diseases (56). In a significant literature, acute respiratory distress syndrome (ARDS) in coronavirus disease

2019(COVID-19) infectedindividuals 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) affectedindividuals, lactate dehydrogenase (LDH) and C-reactive protein (CRP)could indicate lung destruction and could reflect the respiratory distress subsequent to the anomalousinflammatorycondition. A small cohort study of 27 patients, C-reactive protein (CRP)associated with computed tomography (CT)outcomes and led tonoticeablyelevated at the initialphase 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 evaluatelung damage, and computed tomography (CT)results can be beneficial to suggestperniciousresult(56).

Han *et al.* (2020) found thatlactate 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 berelated to the forthrightdestruction 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 linkedto 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 moderatecoronavirus disease 2019 (COVID-19)affected individuals (79). A studyrevealedcorrelation 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 antagonistictherapies 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 biomarkershinting a potent relationship between tissue deterioration and the infectious stage (56).

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

Han *et al*. (2020)made a comparison forlactate dehydrogenase (LDH) with other disease predictingindicatorsinvolvingC-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 elevateddisease predictingreliability 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) infectionshowedelevatedC-reactive protein (CRP), lymphopenia, and raised lactate dehydrogenase (LDH) in seven studies (80). The findings of this meta-analysisdemonstrated that elevated C-reactive protein(CRP), lymphopenia, and higher lactate dehydrogenase(LDH) levels were significantly associated with adverseconditions of coronavirus disease 2019 (COVID-19). The numbers of CD45+ lymphocytes, CD3+ lymphocytes, CD4+ T cells, CD8+ T cells, and CD19+ B cells were noticeablydecreased in coronavirus disease 2019 (COVID-19)affected individuals, and the reduction was more notable in adversecases 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 possiblysuggest anappropriate 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 noticeableproof 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

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