Review

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Potential role of biochemical markers in the prognosis of COVID-19 patients

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Abstract

The global pandemic due to coronavirus disease 2019 (COVID-19) has posed an overall threat to modern medicine. The course of the disease is uncertain with varying forms of presentation that cannot be managed solely with clinical skills and vigor. Since its inception, laboratory medicine forms a backbone for the proper diagnosis, treatment, monitoring, and prediction of the severity of the disease. Clinical biochemistry, an integral component of laboratory medicine, has been an unsung hero in the disease prognosis and severity assessment in COVID-19. This review attempts to highlight the biomarkers which have shown a significant role and can be used in the identification, stratification, and prediction of disease severity in COVID-19 patients. It also highlights the basis of the use of these biomarkers in the disease course and their implications.

Keywords

Biomarkers, clinical laboratory techniques/methods, COVID-19, prognosis

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Introduction

An emerging global pandemic, known as coronavirus disease 2019 (COVID-19), has affected the whole world with the first hit in Wuhan, China.[1] It has been delineated that a proportion of the earlier cases were associated with a seafood market in the city.[2] To date (20 April 2022), the data of people affected by COVID-19 have upsurged to more than 67,405,144 with a death toll of around 1,541,951.[3] The cases are rising in South East Asia with India being the most affected country followed by Pakistan, Bangladesh, and China. Nepal ranks within the top 40 countries affected by COVID-19.[4]

Clinical laboratories continue to play an integral role during this catastrophe. Dedicated clinical laboratories have provided a wide range of involvement in patient screening, diagnosis, prognosis, monitoring, and treatment. In addition, clinical laboratories have also been useful in epidemiological surveillance.[5] This review intends to outline the biochemical laboratory tests that are useful in disease monitoring and assessment of severity in confirmed cases of COVID-19.

COVID-19: The Menace of the Century

The disease is known to be caused by a virus that belongs to the family Coronaviridae. It has, thus, been named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) with high sequence identity (i.e., up to 80%) with the homologous virus which caused the SARS outbreak in 2003 (i.e., SARS-CoV).[6] This is an enveloped virus with a positive-sense, single-stranded RNA genome. It consists mainly of four structural proteins known as Spike (S, which contains the receptor-binding domain, known as RBD), Envelope (E), Membrane (M), and Nucleocapsid (N), along with additional genes such as ORF1a/b, ORF3a, ORF6, ORF7a/b, ORF8, and ORF10.[6,7] It has been postulated that the virus might have emerged as a result of bat spillover, possibly through pangolin as an intermediate animal.[8] As per the endorsement of

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World Health Organization and Centers for Disease Control and Prevention, the definitive diagnosis of SARS-CoV-2 infection is done by molecular biology techniques on upper and lower respiratory materials. The diagnostic technique embraces the meticulous use of real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays, targeting one or more genes in the SARS-CoV-2 genome. A typical RT-PCR procedure for detecting this coronavirus encompasses, in sequence, RNA isolation, its purification, reverse transcription to cDNA, cDNA amplification with RT-PCR instrumentation, followed by (fluorescent) signal detection.[9]

In this period of medical predicament, the clinical laboratory has contributed far from the initial diagnosis and epidemiological surveillance. Laboratory testing, which could be useful in the assessment of the prognosis of the disease, determination of apt therapeutic options, and scrutinizing treatment response, includes routine biochemical, hematological, and immunochemical laboratory tests. Since there is an insidious rise of confirmed COVID-19 cases, this warrants the significant use of laboratory tests that could be used for monitoring the patient and supervision of treatment response.[10] The majority of cases of COVID-19 were associated with mild symptoms and generally with a good prognosis.[11] But, frequently COVID-19 could progress to acute respiratory distress syndrome (ARDS) and eventually can lead to death. Researchers are working relentlessly toward the development of an effective treatment for COVID-19.[12–15]Many new treatment options are available but with a variable success rate.[12–16] Hence, laboratory investigations play an essential role in monitoring the disease, its severity, and the early treatment of the patient.

Immunological response to COVID-19

It has been known that COVID-19 is strongly associated with a belligerent inflammatory response. The exaggerated response leads to the release of a large number of proinflammatory cytokines commonly known as a "cytokine storm (CS)". There is a hyperactive host immune response to SARS-CoV-2 which results in an excessive inflammatory reaction. Few studies have analyzed the cytokine profiles of COVID-19 patients, which depicts that the CS is related directly to lung injury, multiorgan failure, and unfavorable prognosis of severe COVID-19.[17–20] The human system has an effective process to respond to various pathogens. The antiviral response presented normally by the immune system activates the inflammatory pathways of the host's immune system, while a severe disease can occur if there is an embellished or abnormal response of the immune system.[21] During this inflammatory process, cytokines play a critical role. These inflammatory mediators are produced by inflammatory cells such as macrophages, natural killer cells, dendritic cells, and T and B lymphocytes. As in the innate immunity to any viral infection, pattern recognition receptor activity ensues, which recognizes different molecular structures that are characteristic of the invading virus.[22] Literature suggests that severe COVID-19 patients undergo a "CS." This is a life-threatening condition that essentially requires intensive care admission with a high mortality rate. CS is clinically characterized by overwhelming systemic inflammation, hyperferritinemia, hemodynamic instability, and multiorgan failure, and if left untreated, it leads to death. This condition is due to the action of proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-18, interferon-γ, and tumor necrosis factor (TNF)-α.[23] CS has been seen in various viral infections such as influenza H5N1 virus,[24] influenza H1N1 virus,[25] and two coronaviruses highly related to COVID-19: "SARS-CoV" and "MERS-CoV."[26]

Methods

The main aim of this study is to appraise the role of biochemical markers in the prognosis of COVID-19 patients. In this study, we have included the biomarkers such as IL-6, C-reactive protein (CRP), procalcitonin (PCT), ferritin, D-dimer, liver function test (LFT), renal function test, cardiac biomarkers such as cardiac troponin I (cTnI), creatine kinase (CK), CK myocardial band (CK-MB), lactate dehydrogenase (LDH), N-terminal-Pro-Brain Natriuretic Peptide (NT-Pro-BNP), and glycated hemoglobin (HbA1c).

Search strategy and selection criteria

A systematic search was conducted on published studies using Meta-analyses Of Observational Studies in Epidemiology guidelines from January 2020 to December 2021. The authors searched PubMed, Scopus, and medRxiv for observational studies that described laboratory findings of COVID-19 patients following keyword/Medical Subject Headings terms: ((COVID-19 (Title/Abstract)) OR coronavirus (Title/Abstract)) OR SARS-CoV-2 (Title/Abstract). We included those studies in this review that were focused on the laboratory findings and outcomes of COVID-19 hospitalized patients. We excluded studies other than observational studies, an article was written on non-English literature, non-full text, and animal studies.

Study selection

First, we reviewed the abstract and the articles were retrieved and swotted for the availability of data on laboratory findings and outcomes of COVID-19 patients. A total of 59 studies with full text were reviewed and the major findings meeting our objective were included thereafter.

Data extraction

From the included studies, we extracted the following variables relating to laboratory biomarkers and outcomes: IL-6 (pg/mL), CRP (mg/L), PCT (ng/mL), ferritin (ng/mL),

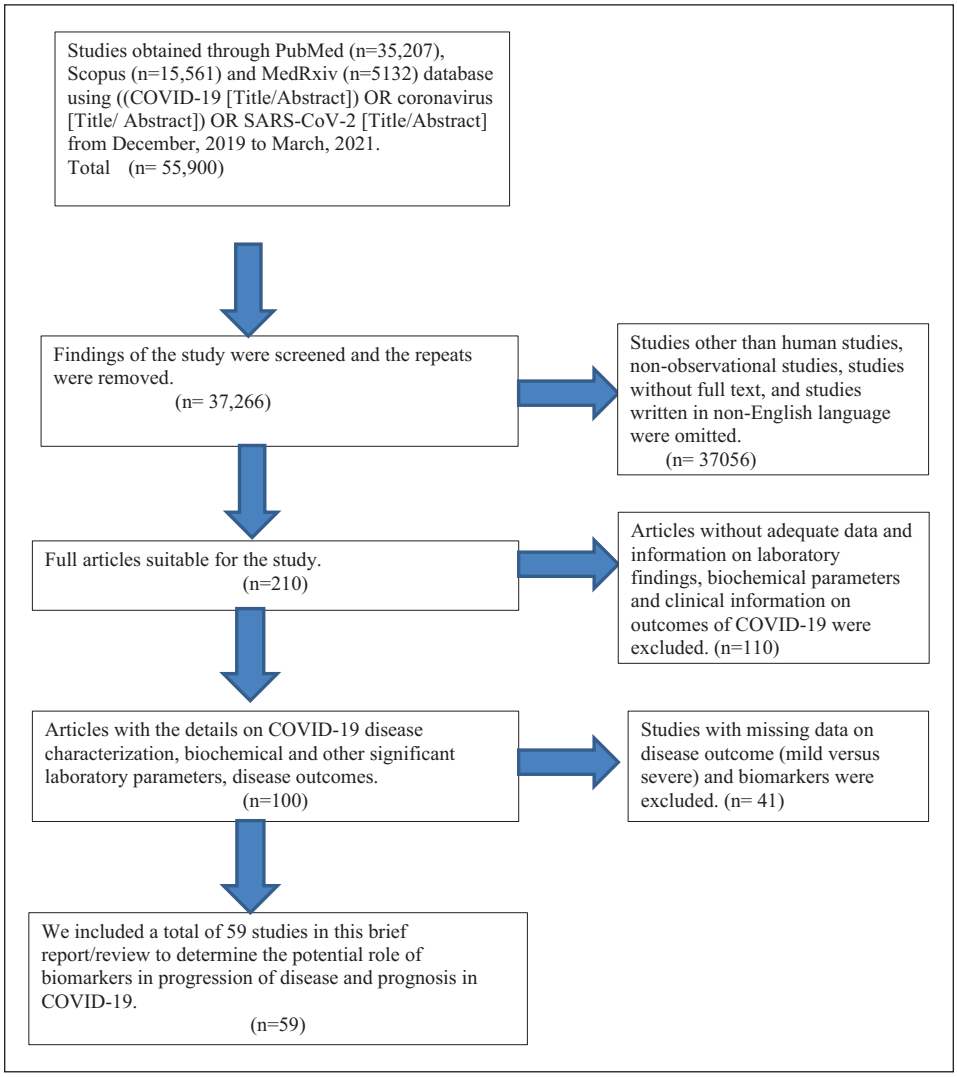

Figure 1. Flow chart depicting the literature search and article selection process of laboratory parameters (biomarkers) and COVID-19 outcomes.

D-dimer (mg/L), aspartate transaminase (AST; U/L), alanine transaminase (ALT; U/L), alkaline phosphatase (ALP; U/L), gamma-glutamyl transpeptidase (GGT; U/L), cTnI (pg/mL), LDH (U/L), NT-Pro-BNP (pg/mL), and HbA1c (%) as shown in Figure 1 respectively.

Biomarkers for monitoring the disease in COVID-19:

1. IL-6: The commonly reported cytokine implicated in COVID-19 is IL-6. Elevated levels of IL-6 are directly associated with higher mortality.[27] Moreover, tocilizumab is a candidate drug to be used in managing the CS accompanying COVID-19. Encouraging results have been reported in China where tocilizumab was used in the treatment of 21 patients with severe and critical COVID-19.[28] Increased IL-6 has been seen in respiratory dysfunction, which implicates a mechanism that might be shared with cytokine-mediated lung damage caused by COVID-9 infection.[29] In addition, the extremely pathogenic SARS-CoV-2 is associated with rapid viral replication and a tendency to infect the lower respiratory tract, resulting in an elevated response of IL-6-induced severe respiratory distress. Thus, studies have recommended that it is plausible for immediate initial evaluation of IL-6 levels upon hospital admission of COVID-19 patients. This attributes to its implication in the assessment of deterioration of the clinical presentation and severity of the disease in COVID-19.[30] IL-6 is assayed using immunoassay techniques, preferably electrochemiluminescence immunoassay. An assay-dependent cutoff value of the reference range up to 7 pg/mL has been determined in normal individuals.[31] A cohort study demonstrated that at presentation, an IL-6 level greater than 35 pg/mL showed high rates of sensitivity to detect patients at risk for respiratory

failure (84% and 95%) with moderate specificity (63%). This study also calculated the cutoff value for IL-6 was slightly lower, that is, 60 pg/mL than the suggested cutoff of 80 pg/mL.[32]

2. CRP: CRP is an acute phase reactant synthesized by hepatocytes in response to inflammation. Increased levels of CRP are seen in bacterial infections compared to viral infections.[33] An elevated CRP level has been reported in COVID-19 patients with higher values seen in severe patients compared to non-severe ones. CRP can be used as a biomarker for disease progression and severity in COVID-19 patients. A recent study has depicted that CRP is significantly associated with disease progression, Receiver Operating Curve (ROC) analysis, and a KM curve confirmed that CRP is a valuable predictor of disease progression in non-severe COVID-19 patients.[33] In addition, the literature suggests that COVID-19 patients with high levels of CRP should be adequately monitored and treated even though their respiratory function indicators do not meet the criteria for severe cases.[33] Normally, CRP is present in plasma at a concentration below 5 mg/L. The concentration of CRP was measured with direct immunoturbidimetric or immunonephelometric assays.[34] Most of the studies have reported the cutoff for CRP as $\geqslant$10 mg/L, although a general agreement has not been established.[35] In patients with COVID-19, the average concentration of CRP is detected to be 30–50 mg/L.[36] IFCC guidelines suggested CRP be included as one of the markers for the evaluation of the severity of infection, prognosis, and therapeutic monitoring.[36] A study from Bangladesh depicted that there were increased levels of CRP in severe COVID-19 patients compared to the non-severe COVID-19 along with other biochemical and hematological abnormalities, respectively.[37]

Studies reported from China suggest that CRP should be assessed along with other clinical parameters for the initial evaluation and follow-up of COVID-19 infection.[35] The cutoff taken was 40–50 mg/L.[38]

3. PCT: PCT is a glycoprotein and a 116-amino acid precursor of the hormone calcitonin. Normally, its synthesis and release occur in thyroid parafollicular C cells. However, during bacterial infection, PCT is also synthesized in many extrathyroid tissues. This abnormal synthesis is mediated by an increased CS mediated by elevated TNFα and IL-6, respectively.[39] Increased PCT levels were seen in bacterial infections and relatively low in viral infections.[40] Hence, this can be used to differentiate between bacterial and viral infections as well. Numerous research studies and meta-analyses have been conducted to determine the efficacy of the use of PCT in the assessment of the severity of COVID-19.[41,42] It has been depicted that raised PCT values were associated with an approximately fivefold higher risk of severe COVID-19.[42–44] Estimation of PCT employs immunoassay techniques like enzyme-linked or chemiluminescence. Cutoff value for PCT was taken as $<$0.5 ng/mL. A meta-analysis that included 16 different studies revealed that an elevated PCT was associated with an increased composite poor outcome which comprised of mortality, ARDS, need for intensive care unit (ICU) care, and severe COVID-19. Moreover, the authors depicted that after pooled analysis of a single cutoff point of $\geqslant$0.5 ng/mL for PCT resulted in a sensitivity of 88% (70–96%) and a specificity of 68% (47–84%).[35]

4. Ferritin: Ferritin is the major intracellular protein for iron storage and plays an integral role in iron metabolism. It has been associated with host protection from pathogen infections.[45] Increased ferritin level is seen in bacterial and/or viral infections, hemochromatosis, and long-term transfusion.[46] Increased ferritin during infection has been attributed to the release of iron in the reticuloendothelial system, the decrease in the ability to transport ferritin in the liver and spleen, and increased synthesis and release of intracellular ferritin.[47,48] Although elevated ferritin level is observed more in bacterial than viral infection,[49] in context with COVID-19, raised ferritin levels might indicate severe secondary bacterial infection. Hence, it can be effectively utilized as a marker for poor prognosis. Moreover, higher serum ferritin level is associated with ARDS, mortality, and severe COVID-19. This may lead to the notion of the presence of secondary hemophagocytic lymphohistiocytosis (sHLH) in COVID-19.[49,50] sHLH is a condition of hyper inflammation characterized by a CS causing fatal multiorgan failure. This condition is most commonly triggered by viral infections, which might lead to the hypothesis of SARS-CoV-2 induces this hyperinflammatory syndrome.[35] Ferritin levels can be assayed using immunoassays, for example, enzyme-linked immunosorbent assay (ELISA), immunochemiluminescence, and immunoturbidimetric assays.[51] The normal reference range for ferritin varies according to age and gender.[51] Researchers have suggested a cutoff of $>$200 ng/mL in COVID-19 patients.[52] A study reported from Bangladesh suggested that among the laboratory parameters along with CRP and D-dimer; ferritin showed good diagnostic performances according to ROC analysis with an AUC value of 0.997 (95% confidence interval (CI): 0.994–0.999; $p < 0.001$) at a cutoff-point 120.5 with 99.7% sensitivity and 82.0% specificity.[37]

5. D-dimer: D-dimers are the wreckages that are produced when plasmin cleaves the fibrin to dissolve the clots. It has been reported that 3.75–6.80% of patients with COVID-19 have elevated d-dimer levels. Generally, the D-dimer assay is commonly done as a routine diagnostic algorithm to exclude the diagnosis of thrombosis.[53] However, increased D-dimer can be seen in various conditions such as deep vein thrombosis/pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation, and conditions such as pregnancy,

inflammation, cancer, chronic liver diseases, post-trauma and surgery status, and vasculitis.[54] In COVID-19 patients, D-dimer is majorly being considered a significant biomarker for clinical outcomes in patients.[55] Rahman et al.[37] demonstrated that increased levels of d-dimer along with CRP and ferritin are a good indicator to evaluate the severity of COVID-19. Similarly, they also reported that the severe COVID-19 patients showed significantly higher d-dimer compared to non-severe COVID-19 patients, respectively.[37] A study reported by Zhou et al.[55] revealed that D-dimer $>1\,\mu g/mL$ is a risk for mortality. Yao et al.[53] depicted that a cutoff value of 2.14 for D-dimer levels upon admission for in-hospital mortality has an AUC of 0.846. The sensitivity and specificity are 88.2% and 71.3%, respectively. The findings of this study suggest that an elevated D-dimer level on admission ($>2.14\,mg/L$) may identify the patients at higher risk for in-hospital mortality and therefore inform physicians about suitable candidates for intensive care and early intervention.[53] D-dimer elevation indicates the state of hyperfibrinolysis state and increased inflammatory burden induced by SARS-COV-2 infection.[53] D-dimer is assayed by immunoturbidimetric assay and the reference range is 0–0.50 mg/L.[53]

6. LFT: Abnormalities in LFT parameters could be used as a predictor for monitoring the severity of the disease. A research study has shown that 90% or more of the COVID-19 patients with abnormal liver tests were mild at admission (i.e., with $<2\times$ Upper limit of normal (ULN), and about 24% of them developed increased ALT and GGT levels to substantially more than $3\times$ ULN during hospitalization.[56] Patients with elevated liver enzymes at admission or during hospitalization have shown significantly higher odds of progressing to severe COVID-19. In addition, the use of antiviral drugs, especially lopinavir and ritonavir, has been shown to increase the odds of liver injury by fourfold.[56] Hence, the patient needs to be intently monitored under these specific therapies with special attention to patients who had abnormal liver test results at admission.[56] GGT and ALP are commonly considered cholangiocyte-related enzymes. However, in severe COVID-19, GGT remains the single elevated enzyme which delineates the fact that the damage is likely drug induced rather than bile duct injury.[57] The postulated mechanisms for liver damage in COVID-19 are immune-mediated damage due to the severe inflammatory response following infection, direct cytotoxicity due to active viral replication in biliary epithelial cells which express angiotensin-converting enzyme 2 (ACE2), and hypoxic hepatitis due to anoxia, and drug-induced liver injury, respectively.[58] Since the course of the disease caused by the novel virus is uncertain, a consensus for the exact liver injury classification is lacking. However, commonly practiced liver abnormalities have been defined as the elevation of hepatic liver enzymes in serum: ALT >40 U/L, AST >40 U/L, GGT >49 U/L, ALP >135 U/L, and total bilirubin >1 mg/dL, respectively.[58] Hence, LFT should be routinely investigated to assess the ongoing hepatic injury and monitor the disease severity in COVID-19, principally in patients under antiviral treatment.

7. Renal function test: Acute renal impairment has been one of the findings in the previous SARS epidemic in 2002–2003. During that period, it was reported that 6.7% of patients developed acute renal impairment/acute kidney injury (AKI) with a tremendously high mortality rate of 91.7%.[59] In this recent pandemic of COVID-19, a low prevalence of AKI with the range of 0.5–19.1% has been reported.[60–62] Currently, AKI detection is principally dependent on the acute changes in serum creatinine.[60–62] As per the findings reported by Cheng et al.,[60] elevated baseline serum creatinine in patients with COVID-19 was likely to be admitted to the ICU and undergo mechanical ventilation. Hence, this necessitates the early identification and treatment of kidney deterioration, including adequate hemodynamic support and limiting nephrotoxic drugs, and increased frequency of creatinine testing or other kidney markers. Albumin levels (serum and urine) and serum total protein estimation can be used as predictive markers in COVID-19. The major mechanism of renal injury has been implicated as inflammation and damage within the renal system caused by cytokine inflammatory response to infection, the direct impact of cytokine release on renal tissues, and organ cross-talk (e.g., cardiomyopathy and acute viral myocarditis can contribute to renal vein congestion, hypotension, and renal hypoperfusion).[62]

8. Cardiac biomarkers: Cardiovascular events were commonly observed in severe COVID-19 patients.[63–66] Some of the mechanisms proposed for cardiovascular complications in COVID-19 are viral myocarditis, injury to the myocardium, cytokine-driven myocardial damage, microangiopathy, and exacerbation of coronary artery disease.[64] While this mechanism is postulated, none of them is proven.[10] A preliminary study published by China Initial reported a total of 12% of all patients and 31% of ICU patients had an acute myocardial injury, as evident by increased cTnI levels.[19] Researchers have emphasized that high cTn values were predictive of admission to intensive care[19] and showed higher in-hospital mortality.[67,68] There are two different schools of thought in the assessment of cardiac biomarkers in COVID-19 patients. Recently, the American College of Cardiology published a statement on the role of cardiovascular biomarker monitoring in patients with COVID-19, which states that "clinicians are advised to only measure troponin if the diagnosis of acute myocardial infarction is being considered on clinical grounds."[68] This statement is largely implied to evade unnecessary laboratory tests in COVID-19 patients and consequently reduce the consultation and procedures which comprise

bedside echocardiography and angiography.[68] While the other groups of researchers suggest that cTnI cannot be exclusively considered a binary test for diagnosing myocardial infarction, but a useful prognostic indicator of both ischemic and non-ischemic causes of cardiac dysfunction that can be extremely helpful in patient triage and proper treatment selection.[69] cTnI is an established gold-standard necrotic biomarker for the assessment of myocardial risk. It is released in the myocardium, specifically in the presence of myocardial injury. CK-MB and BNP are other commonly used diagnostic biomarkers of myocardial injury. These biomarkers have shown the potential to assess the severity of symptoms in COVID-19. The reference ranges for these biomarkers are variable, with the commonly considered range of cTnI = 0–28 pg/mL, CK-MB = 0–24 U/L.[70] A common method used for the determination of cTnI and BNP is immunoassay-based methods (ELISA, Chemiluminescence Immunoassay (CLIA)) and CK-MB are immune inhibition or immunoprecipitation, electrophoresis, and column chromatography.[71–73] Thus, this clearly outlines the imperative role of biomarkers like cTn and natriuretic peptides as a predictive marker for the progression of the disease and hence helps inappropriate patient risk stratification.[10]

9. Lactate dehydrogenase: LDH is an old enzyme, that belongs to the transferase class of the enzyme, and catalyzes the reversible oxidation of L-lactate to pyruvate with the mediation of NAD^+ as a hydrogen acceptor.[74] LDH activity is shown in the cytoplasm of many cells of the body, and enzyme concentrations in various tissues are about 1500–5000 times greater than those physiologically found in serum. Leakage of the enzyme in a small amount of damaged tissue would lead to a significant increase in the serum activity of LDH. LDH has depicted a wide range of distribution and increased the number of diseases. However, today, its implication has been limited to oncology.[67] LDH is being used as a diagnostic marker in hemolytic anemia and has also been useful in the prognosis of acute and chronic complications.[75] Increased LDH has been seen in megaloblastic anemia, Hodgkin's disease, multiple myeloma, and germ cell tumors.[76–78] Increased LDH in serum is due to the hypoxic condition as seen in tumor and necrosis-related events. During this COVID era, the LDH level had shown a resounding association with the severity of COVID-19.[79] Increased LDL levels depict two consecutive events, that is, direct lung damage and more widespread tissue injury.[79,80] A study reported by Aloisio et al.[81] depicted that the best variables for death prediction using multivariate logistic regression were patient age, LDH, and albumin concentrations.[80] They further elaborated that markedly altered levels of these two laboratory parameters describing a general impairment of the patient's health status and organ function independently predicted death during hospitalization. Among the various parameters that showed the higher power for excluding the need for intensive care, LDH secured the position as a predictive biomarker strongly with an AUC of 0.88–0.89. Moreover, the researchers illustrated that the possible role of LDH as the most powerful clinical predictor of outcome worsening in COVID-19 patients was delineated by the fact that this test is the only biomarker that remains significantly associated with both selected outcomes in the multivariate logistic regression analysis. Increased LDH concentration associated with low serum concentrations of albumin was significantly associated with higher odds of death (odds ratio (OR), 161.5 (95% CI: 2.28–11,422.8; $p = 0.019$), while low LDH activities were associated with lower odds of ICU admission (OR, 0.06 (95% CI: 0.01–0.54); $p = 0.011$]. The best LDH cutoffs were >731 U/L, associated with a positive predictive value (PV) of 0.84 (95% CI: 0.70–0.93) and a positive likelihood ratio (LR) of 19.7 (95% CI: 9.1–42.7) for death prediction, and <425 U/L, associated with a negative PV of 0.99 (95% CI: 0.97–1.00) and a negative LR of 0.10 (95% CI: 0.03–0.30) for intensive treatment, respectively.[81] The benefit of estimation of LDH levels is the ease of assay through easily available commercial kits.[82] Although LDH seems to be a commonly assayed test in most primitive with sophisticated laboratory setup, the significance of the LDH results in COVID-19 patients lacks the standardization of the methods.[83] There is a paucity of data, as there is no sufficient literature that provides complete information on cutoff and validation of LDH in COVID-19 patients.

9. Other biomarkers of significance:

i. **NT-Pro-BNP:** NT-Pro-BNP belongs to the natriuretic peptide compound which is used as the marker of myocardial strain.[83] Increased NT-Pro-BNP level is seen in patients with severe respiratory illnesses, predictably in the absence of elevated cardiac filling pressure or clinical heart failure.[84,85] In addition, a higher NT-Pro-BNP level is significantly associated with adverse outcomes in ARDS patients. This peptide is released in the circulation following stress to the myocardial cell wall along with inflammatory molecules such as lipopolysaccharide, IL-1, CRP, and corticotrophin, independent of ventricular function.[86] A Chinese study depicts a strong correlation between NT-pro-BNP levels and increased risk of mortality in hospitalized patients with COVID-19.[86] CKD patients were found to be more likely to be admitted to the ICU and undergo mechanical ventilation. Hence, this insinuates that acute or chronic kidney disease embodies an increased risk for deterioration and detrimental clinical outcomes in COVID-19.[87] It has been proposed that SARS-CoV-2 binds to the ACE2 receptor, which is found in human kidneys, thereby signifying that the kidneys may be a direct target of the virus.[88] A second probable mechanism is superimposed pulmonary edema due to impaired fluid excretion. In

addition, to date, limited treatment preferences for COVID-19 in patients with renal impairment were available owing to the lack of safety data among these patient groups. All of these discoveries are directly related to a few previous studies which have demonstrated that there is an increased risk of death due to kidney injury in patients with influenza A virus subtype H1N1 and SARS[89,90] and even in recent studies in patients with COVID-19 infection.[91] Moreover, researchers have proposed that the COVID-19 virus directly infects human kidney tubules and induces acute tubular toxicity through different direct and indirect paths that result in tubular pathophysiology.[92] NT-Pro-BNP was assayed using ELISA or electrochemiluminescence immunoassay.[93,94] The values are assay dependent.[92,93] The most commonly taken range is <100 pg/mL as normal values and >100 pg/mL suggestive of heart failure.[85,92,93]

ii. **HbA1c:** HbA1c is highly recommended as a long-term glycemic indicator in patients with type 2 diabetes mellitus (T2DM).[94] Raised HbA1c has a direct impact on the increased risk of hospitalization in T2DM patients due to pneumonia.[95] A study reported by Al Hayek[96] from Saudi Arabia demonstrated that increased glycosylated hemoglobin levels as a major risk factor for inpatient admission in diabetic patients infected with COVID-19. A study from Wuhan suggested that raised glycosylated hemoglobin level is associated with inflammation, hypercoagulability, and low SaO_2 in COVID-19 patients.[97] Studies done in the past have shown a direct relationship between glycemic control and COVID-19. This has highlighted an association between in-hospital glucose levels and disease severity. Despite the rigorous control of hyperglycemia, it has not shown significant improvement in hospitalized patients in conditions other than COVID-19.[94,98] Thus, suggesting hyperglycemia as a biomarker for the severity of the disease and deteriorating health status rather than having an actual causative effect.[94,98]

Limitations

There are a few limitations of this review which include the incorporation of heterogeneous studies. This article was intended to explore the potential biochemical markers that could be useful in monitoring the disease in COVID-19 which will also aid in the prediction of the outcome. Thus, other integral parameters such as neutrophil/leucocyte ratio, QT elevation, and various hematological and serological markers could not be included. We could not find enough data/information on the varying levels of the biomarkers during the COVID-19 course which could have a potential impact as a predictor of the disease. Though the facts and figures for COVID-19 are changing every day, we collected this information for this brief review to provide adequate information to the laboratory professionals and clinicians to determine the appropriate biomarker for risk stratification and prediction of disease course in COVID-19 patients. As this review anticipates highlighting the possible and applicable biochemical markers useful in COVID-19, the findings are represented accordingly.

Conclusion

Clinical biochemistry is considered a cornerstone of laboratory medicine and encompasses a wide range of applications in health services. Biomarkers of prognostic significance such as IL-6 and PCT, although expensive, have shown exquisite clinical implications for ineffective management, monitoring, and assessment of the severity of disease in COVID-19 patients. In a resource-limited setting like ours, it is difficult to undergo the assessment of most of the biomarkers, especially in the rural setting. Hence, simple and cost-effective markers such as CRP, LDH, and HbA1c could be used for monitoring the severity of COVID-19 infection. The meticulous use of the significant biomarker could be helpful for ineffectual patient management and delivering quality patient services.

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Authors' contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit it to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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